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care and cure

Many current concepts of the fundamental characteristics of malignant tumors have been derived from studies of cancer of the breast in animals and man. The accessibility of the breast ideally adapts it to observation of spontaneous and induced changes. Effects of surgical, radiological, chemotherapeutic, hormonal, and genetic procedures are most conveniently observed in this organ. Most of what is known concerning heredity of neoplastic disease evolved from observations of breast cancer.

Cancer of the breast was the first malignant tumor found to be associated with its hormonal environment. Under endocrine influence the breast, like the prostate, has been utilized advantageously in developing hormone therapy of cancer—gonadectomy, hormone administration, adrenalectomy, and hypophysectomy.

A carefully planned therapeutic approach to the patient with carcinoma of the breast involves study of the histological, clinical, and biological types of the tumor, the state of its progression, and its reaction to hormone therapy.

There is a wide difference in expert opinions concerning optimal therapy. Should breast surgery be minimal—simple amputation with or without irradiation, or should it be maximal—the conventional Halsted operation with dissection of the axilla and removal of the pectoralis major, the more radical mastectomy with internal mammary node excision and supraclavicular dissection, or the more mutilating superradical attack upon these structures by division of the first rib and elevation of the clavicle? Unequivocal answer to this question is not yet available. Careful statistical analysis of the data now rapidly accumulating in tumor registers will eventually yield the answer.

Despite these differences of opinion, the greatest present hope for cure of cancer of the breast, as of other sites, rests in early diagnosis and prompt treatment.

Though it is cure we seek—and frequently attain in the early lesion—this should not dominate our clinical planning. There is much to be offered in *care* even when *cure* is unattainable.

*Cover—Detail from Battle of the Amazons by Peter Paul Rubens (1577-1640).
Alte Pinakothek, Munich. Reproduced by permission of Harper & Brothers.*

Women of this legendary race had their right breasts seared off in infancy in order that, in adulthood, the breast might not interfere with the use of the bow, the spear, the axe, and the half shield in war, or with the javelin in hunting. For their lack of breasts they were called Amazons.

The Amazon River takes its name from the fighting women savages encountered by the Spanish explorer, Orellana in 1541.

As late as the 19th century similar breast mutilation was practiced by the Christian sect of fanatics in Russia and Rumania, called from their practice of ritual castration, Skoptsi.

These legends and practices possibly

account for the rumored mastectomies among the women soldiers of tsarist Russia, supposedly designed to facilitate the use of more modern weapons by these modern Amazons.

In direct contrast to these he-woman military practices, is the recent report of the tough Army colonel whose WAC detachment obtained superior inspection rating following his order for the use of "falsies" by the hypomastics in his unit.

Mastectomy is the conventional therapy for cancer of the breast; and it has even been suggested as prophylaxis for cancer in older women, under certain conditions.

NEWSLETTER

JANUARY, 1958

Typical of the 1581 papers presented at the American Institute of Biological Sciences at Stanford University, Stanford, Calif., in late August were:

Diller (Institute for Cancer Research, Phila.) reported isolating from the blood and spleen of leukemic C58 mice an acid-fast organism with a complicated life history similar to that of the avian tubercle bacillus. One part of the life cycle is marked by the presence of minute acid-fast "granules." Cultured and injected into leukemia-resistant strains of mice, these organisms wrought changes in liver cells, including multiple, intranuclear inclusion bodies. In earlier work, similar organisms were isolated from azo dye-induced hepatomas; and these produced the now familiar changes when injected into the liver. The big questions are whether the inclusion bodies are filtrable forms of the organisms, whether they are indeed the cancer and leukemia producers, and whether they might be the "viruses" reported by other investigators.

Androgenic hormone quickly enabled juvenile male lizards, which attack males and females alike, to distinguish between the sexes, Evans (Albert Einstein College) reported. Treated animals continued to challenge male intruders, but they courted willing females.

Hisaoka (Loyola, Chicago) has found that the hepatocarcinogen, 2-AAF, is abortive when ovoviviparous fish are exposed to it. In strong concentrations, it induced abortion in 20 minutes; in weak concentrations, it retarded growth and differentiation, and delayed abortion as late as twenty-five days following exposure.

Hummel (Bar Harbor) transplanted the ovaries of genetically obese and presumably sterile mice into castrated non-obese mice. When the recipients were mated to non-obese males, four transplanted obese ovaries produced sixty-three viable young, thirty of them obese and thirty-three heterozygous for obesity. One grafted female bore four obese young when mated to a heterozygous, obese male. The transplant technique enables mouse-growers to produce large quantities of obese mice.

Lein (Northwestern) has demonstrated that white

light catalyzes the activation of thyroxin in liver tissue. Following exposure to light, thyroxin-rich liver-oxidation rates rise significantly. The investigator interprets these and other results as indicating that thyroid hormone exists in a storage form (thyroglobulin), a circulating form (thyroxin), and an active form (an oxidation product, probably the semiquinone).

Maher and Levedahl (UCLA) have found no oxygen-consumption differences in thyroidectomized, thyroxin-treated, and normal lizards (Anolis carolinensis) and have concluded that the thyroid is not important in the oxidative metabolism of this animal.

Female mice were made much more susceptible to audiogenic seizure after being given 1.5-2 r. Radiation did not change the seizure incidence in males, however, in tests conducted by Miller (U. of Chicago). The tests help explain an earlier casual observation: Mice housed near radiation sources became more seizure susceptible; moved away, they became less susceptible.

O'Brien and others (Marquette) irradiated the exteriorized blood stream as it coursed through a short arc of polyethylene tubing. Preliminary results in two dogs and four rabbits showed elevated white counts for three months and, at autopsy, enlarged spleen, marrowless and brittle sternum, pink and very fatty femur marrow, hypertrophied adrenal cortex, and atrophied medulla.

Williams (Harvard) has isolated, in a highly purified form, the "juvenile hormone" which prevents metamorphosis in insects. It is a relatively small and stable molecule.

Phillips, Braun, and Plescia (Rutgers) have produced specific antibodies against DNA. Bacterial DNA was injected into rabbits. The antibodies against bacterial DNA reacted with DNA from other species, but on a descending scale as phylogenetic relationships weaken. This basic finding may have bearing on several kinds of DNA and virus studies and raises again the question of whether cancer-specific antibodies can be produced.

What determines the life span of various species? Sacher (Argonne) advances the theory that brain size is involved. He reasons that animals with larger brains have greater ability to regulate metabolic rates. Because man has a large brain, he should -- and does -- have superior metabolic regulation and hence longer life. A study of

(Continued after Page 36)

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Keeping up

Etiology of Mouth Cancer

Analysis of 659 cases of cancer of the oral cavity showed a predominant incidence in men, and that at present the incidence in men is decreasing slightly while in women it is increasing. Of 543 men with cancer of the mouth only 3 per cent had never smoked in contrast to 10 per cent of the controls, whereas 29 per cent were excessive smokers as compared with 17 per cent of the controls. Cigar and pipe smoking increased the risk of oral cancer more than cigarette smoking. Tobacco chewing was of lesser etiologic significance. Among the women there were twice as many nonsmokers among the controls as among the study group, and three times as many chain smokers with cancer of the mouth as among the controls. Alcohol consumption is also a significant etiologic factor. Of the male patients, 33 per cent drank seven ounces or more of whiskey a day as compared with 12 per cent of the controls. Syphilis, or its arsenic therapy, was significant in cancer of the lip and the anterior two thirds of the tongue. Dental irritation and trauma were not found to be significant. The incidence of oral cancer in the United States today is consistent with the factors of tobacco and alcohol consumption—increase in cigarette smoking by both men and women, decrease in cigar and pipe smoking, and decrease in tobacco chewing. Exposure to sunlight is an additional factor in cancer of the lip. Four out of five cancers of the mouth in this country are preventable. This study shows that environmental factors play a role in the development of cancer. The intrinsic factors regulating the formation of cancer remain unknown at present. Research in epidemi-

ology and preventive medicine, directed toward the control of the extrinsic factors, can successfully curtail the incidence of various types of cancer, including that of the oral cavity.

Wynder, E. L.; Bross, I. J., and Feldman, R. M.: *A study of the etiological factors in cancer of the mouth.* *Cancer* 10:1300-1323, Nov.-Dec., 1957.

Sigmoidoscopy

More and more general surgeons, internists, and general practitioners are training themselves to perform anorectocolonic endoscopy. Every physical examination should include endoscopy, preferably without preliminary preparation, for at least 15 cm. from the anal margin. Sigmoidoscopy does not require a proctologist. The only real contraindication is obstruction preventing introduction of the instrument, including unyielding angulation of the bowel. It is also wise to discontinue sigmoidoscopy because of the struggles of a nervous, uncooperative patient. In more than 60 per cent of adult and juvenile patients no preliminary preparation is necessary. Irrigations may wash away blood or pus descending into the sigmoidoscope from above its reach. If feces make the examination unsatisfactory, the patient is asked to return after proper preparation, or a concentrated enema is given and the patient is reexamined in 15 to 20 minutes. If anesthesia is to be used the patient is always given preliminary preparation. Cathartics and suppositories are contraindicated. Simple enemas of lukewarm water or saline solution are satisfactory. Anesthesia is used in sigmoidoscopy of children less than five years of age and in the presence of painful anal lesions, such as fissure. Sedative

with Cancer



premedication is usually unnecessary. During sigmoidoscopy without anesthesia the examiner should maintain a continuous conversation at the level of the patient's intelligence. Digital examination should always precede endoscopy. Complications sometimes following sigmoidoscopy are peritoneal irritation, perforation, bleeding, anal irritation, superficial anal laceration and abdominal discomfort or pain. Biopsy should be performed on all suspicious lesions seen at sigmoidoscopy, the lesions being removed in toto when possible. Cancer cells may be clustered in the very depth of the lesion. Biopsy should be deep enough to include tissue at the base of the lesion. Fractional biopsy of an adenoma, removal of bits of tissue from its summit, is condemned.

Turell, R.: Sigmoidoscopy (conventional). S. Clin. North America 1261-1281, Oct., 1957.

Treatment of Carcinoma in Situ

The relationship of carcinoma in situ of the cervix to invasive clinical cancer is not fully appreciated by all who are concerned with the care of patients with cervical cancer. As a result of failure to accept the serious potentialities of this lesion some physicians have recommended and carried out treatment which falls far short of adequate therapy, namely, complete removal of the uterus. Many years will be required for adequate evaluation of the complete and the more conservative treatment; but even now there is sufficient evidence upon which to base intelligent therapy. A considerable length of time is required for the serial changes from normal cervical epithelium, through basal-cell hyperactivity and intraepithelial cancer, to invasive cancer. In a high percentage of

patients who have actually developed cancer, it can be shown that intraepithelial carcinoma pre-existed. The diagnosis of cervical carcinoma in situ must be made on strict microscopic criteria, or many needless hysterectomies will be performed. Carcinoma in situ develops into invasive cancer sufficiently frequently to justify prompt hysterectomy. When the patient is pregnant at the time of diagnosis, she may usually complete her pregnancy. Unequivocal diagnosis of cervical carcinoma in situ is an indication for prompt hysterectomy with removal of a generous vaginal cuff. In discussion, Martzloff (Portland) stated that failure to observe co-existing cancer explains most of the unsatisfactory experiences with cancer in situ, and that the surgical procedure recommended seems to fall far short of an accepted operation for cancer. Morton (Los Angeles) classifies these early growths as Stage 0, which he defines as that circumstance in which there is microscopic cancer only, confined to the superficial several millimeters of the cervical stroma as evidenced in a cone biopsy. Many cases diagnosed as carcinoma in situ in the past must remain in an uncertain classification because frankly invasive cancer was not ruled out, not enough tissue having been examined to make the exclusion. When diagnosis is made in this manner it is possible to be conservative in certain instances, e.g., in young women who desire children and who are cooperative in follow-up study. Peighal (New York) preferred to use the cytologic smear to indicate the need for biopsy study.

Te Linde, R. W.; Galvin, G. A., and Jones, H. W., Jr.: Therapy of carcinoma in situ; implications from a study of its life history. Am. J. Obst. & Gynec. 74:792-799; disc. 799-803, Oct., 1957.

Cancer-Cell Seeding

Apparently, cancer-cell seeding occurs in one-fourth or more of operations for malignant neoplasms. Operative wounds were washed with saline and the washings were examined for tumor cells. Comparisons were made between patients known to have cancer and those known to have other diseases, and the method was found to be 91 per cent accurate. Among 113 cancer patients studied, tumor cells were demonstrated by wound washing in 27 per cent and in 14 per cent the findings were considered suspicious. In patients with positive washings, seven known seeded recurrences were later observed in the operative areas; an additional two recurrences were seen in patients with suspicious washings. Recurrences also have been detected in seven patients whose washings were negative for tumor cells. Proof that wound seeding sometimes causes treatment failure has stimulated a search for substances which can be used to destroy cancer cells in the wound. In animals, formaldehyde has been the most effective of the substances tested; ethyl alcohol, sodium citrate, sodium carbonate, and hypertonic saline also diminish incidence of implants.

Smith, R. R., and Hilberg, A. W.: Cancer-cell seeding of operative wounds as a cause of failure in the surgical treatment of cancer. J. Maine M.A. 48:151-156, Jan., 1957.

Ovarian Cancer

Million-volt roentgen irradiation is of palliative value in advanced carcinoma of the ovary. Results are best when a tumor dose of 3000 to 5000 r is given in three to six weeks. Some relief is afforded by radiotherapy to about two-thirds of patients with advanced ovarian adenocarcinoma. Average duration of improvement is about nine months. Effects of radiation include the relief of pain, increased strength, improvement in gastrointestinal and urinary function, reduction of ascites, relief of intestinal obstruction, and, rarely, tumor shrinkage. Effect of irradiation does not vary significantly with histologic tumor type. Super-

voltage roentgen irradiation appears to be preferable to 200- to 250-kilovolt radiotherapy because (1) a greater depth dose can be delivered in relation to skin dose, (2) the skin tolerates supervoltage radiation well, (3) fewer systemic effects occur, (4) the distribution of radiation is more uniform, and (5) use of multiple small ports and consequent dangers of overlapping and separation of fields are avoided. Most patients treated through pelvic or small abdominal ports tolerate treatment well. Irradiation of the whole abdomen may produce nausea, vomiting, diarrhea, and weakness, but side effects are rarely so severe that treatment must be stopped. Erythema and dry peeling of the skin are common; moist desquamation is infrequent and is usually limited to the inguinal and gluteal folds.

Chu, F. C. H.: The results of treatment of ovarian cancer with one million volt x-ray. Surg., Gynec. & Obst. 104:45-52, Jan., 1957.

Chemical Carcinogens

The author has worked on carcinogens for the past twenty-five years and is now occupied with the identification of the carcinogenic factors of tobacco smoke and of atmospheric pollution in the laboratory of the new Medical Research Council Carcinogenic Substances Group at the University of Exeter. Pott in the latter part of the eighteenth century attributed chimney-sweep's cancer to soot. In 1915 Yamagiwa produced skin tumors on the ears of rabbits. In the 1920's employees in the Scottish shale-oil industry and mule spinners in the Lancashire cotton industry were found to have skin cancers from exposure to oils. Kennaway in 1930 first produced cancer by pure chemical compounds. The parent compound was 1,2-benzanthracene. In the fractionation of coal tar a very potent carcinogenic hydrocarbon, 3,4-benzpyrene, was found. The carcinogenic hydrocarbons, applied to the skin of laboratory animals, first cause papillomas and then malignant tumors that show invasion of muscle and give rise to secondary tumors, usually in the lungs or in the axillary lymph nodes.

Carcinogenic activity is not confined to polycyclic hydrocarbons but is also found in many analogous compounds in which the aromatic rings contain sulfur or nitrogen. Carcinogens are of widely different chemical types with no common features, such as the azo dyes and the aromatic amines. The carcinogenic hydrocarbons act locally at the site of direct application. Applied to the skin they induce squamous-cell epitheliomas; injected into the subcutaneous tissue they give spindle-cell sarcomas; and tumors have been obtained by direct application of these hydrocarbons to liver, spleen, brain, and bone. The azo dyes probably act indirectly by conversion in the liver into aromatic amines. One of the aromatic amines, β -naphthylamine, causes cancer of the bladder in dogs and is the probable cause of bladder cancer among workers in the dye industry. Other known carcinogens are certain epoxides (diepoxide of vinylcyclohexane), some ethyleneimides, and the nitrogen mustards—all acting as cytotoxic agents on the chromosome mechanism as do roentgen rays. The author suggests that the polycyclic hydrocarbons may transform normal cells into cancer cells by becoming firmly attached to skin proteins, similarly to the way in which the azo dye, butter yellow has been shown to combine with liver proteins. Malignant change may, therefore, be attributable to deletion of proteins essential for growth control. Of the present search for the carcinogens of cigarette smoke and of polluted air the author states that conclusive evidence of the relative and absolute importance of the various factors is going to be very difficult to obtain. In the meantime the best advice, especially to young people, is that it would be well to avoid the large individual cities, and to give up smoking. A frank speculation is presented that cholesterol may play an important part in the etiology of cancer. The closely related methylcholanthrene is a very powerful carcinogen, and cholesterol itself in various degrees of purity has caused cancer in mice. Even the carcinogenic action of sunlight may be mediated through a cholesterol derivative, as provitamin D. Study of chemical carci-

gens is likely to prove one of the most profitable forms of cancer research and to give increasing insight into the nature of malignant change. The better understanding we achieve of the nature and origins of cancer the better able we will be, just as with individual forms of cancer, to prevent all forms of this disease. The impressive advances of knowledge of cancer in the past half-century justify the hope of eventually reaching the goal.

Cook, J. W.: *Chemical carcinogens and their significance*. *Lancet* 1:333-335, Feb. 16, 1957.

Radiosensitivity of Cervical Cancer

The behavior of basal-cell activity before and during treatment suggests that it serves as an index of host resistance. Sensitization response differs from radiation response only in regard to the inciting factor. Radiation response is a more accurate evaluation of the success of radiation therapy and in radiation response a satisfactory basal-cell response represents the real effort on the part of the host to control the disease. A good basal-cell response ranges from 45 per cent and over while a poor response is found below 30 per cent. A progressively increased basal-cell response during the course of therapy signifies favorable prognosis better than do any set figures. In a typical smear showing good sensitization response the prevailing change is vacuolization followed next in frequency by nuclear changes. These changes take place in all layers of the cervical epithelium but earliest and most markedly in the basal layers, and infrequently in the cornified layers. Thirty patients under treatment for carcinoma of the cervix were studied by serial smears before, during, and after therapy. Cellular changes commonly considered to be evidence of radiation effect were found in the pre-irradiation smears. Clinical regression of the lesion is more closely related to good basal-cell response than to any other findings.

Smith, C. J.; Stepto, R. C.; Schaack, C. B., and Schmitz, H. E.: *The evaluation of the basal cell in the radiosensitivity studies of carcinoma of the cervix*. *Am. J. Obst. & Gynec.* 73:598-606; disc. 606-608, March, 1957.

Multiple Gastric Cancers

Forty cases of multiple, simultaneous gastric cancers were seen at the Mayo Clinic during a ten-year period. These forty cases represented 2.2 per cent of all gastric cancer seen during that period. Two additional cases of multiple, nonsimultaneous gastric cancers were seen during the period. Three of the forty-two patients had pernicious anemia and four gastric polyposis. Two patients had one or more malignant tumors unrelated to the multiple gastric cancers. It may be assumed that a considerable proportion of gastric cancers have multicentric zones of malignant change at some time in their development. The incidence of multiple lesions is justification for the opinion that total is superior to subtotal gastrectomy in treatment of carcinoma of the stomach and for "second-look" operations.

Moertel, C.G.; Borgen, J.A., and Soule, E.H.: Multiple gastric cancers: review of the literature and study of 42 cases. *Gastroenterology* 32:1095-1103, June, 1957.

Mechanism of Radiation Response

• Aside from the hormone effect on metastases of carcinoma of prostate, radiation—from radium or from the roentgen tube—is the only known agent with any destructive effect on the growth of malignant tumors. The manner in which radiation acts remains a mystery after fifty years of such use. Clinical experience with radium needles has demonstrated that best results are obtained when the radium is put into the healthy tissue surrounding the growth. This suggests to the author that radiation, acting on normal cells, alters their metabolism so that they produce substances antagonistic to the agent which causes cancer (in all probability a virus), or to the cells which have been altered by the cancer agent, and that these substances, carried by the lymph stream to the area of the growth, cause death of the cancer cells. Since irradiation of a tumor has no effect upon distant metastases, these substances, if they exist, would seem to be destroyed before they reach the general circulation. This possibility, that can-

cer is cured by a response of normal tissues to radiation, should be given more attention. An investigation of what is taking place would be more likely to give results than the random testing of drugs, none of which to date has caused tumors to disappear as has radiation. Several lines of research are indicated.

Pannett, C. A.: The response of malignant tumours to radiation; a hypothesis. *Lancet* 1:829-830, April 20, 1957.

Carcinoma of the Prostate

The results of radical prostatectomy pioneered by the late Hugh Young and so ably developed by men like Belt and Jewett and others have been excellent in those cases where early lesions have been found. Approximately 15 per cent of men more than 55 years of age have cancer of the prostate; 5 per cent of these men eventually die of this disease. The etiology of prostatic cancer is obscure but it is apparently unrelated to infection or hyperplasia. All men older than 50 years should have a rectal examination at least yearly. Early diagnosis of prostatic cancer is made only by biopsy of the suspicious area noted on rectal examination. Biopsy is obtained by perineal punch, transrectal punch, transurethral punch, or by open perineal or open retropubic approach. If the cancer has spread beyond the prostatic capsule only palliation can be expected from treatment. Palliative therapy includes castration, estrogen therapy, adrenalectomy, hypophysectomy, and transurethral resection. Retropubic radical prostatectomy makes cure possible and affords a good look at the area of potential extracapsular spread. Approximately 30 per cent of patients with cancer of the prostate have local and regional lymph-node metastases without an elevated acid phosphatase level or evidence of bone involvement. Irradiation with radioactive gold injected directly into unresectable cancer tissue is worthwhile. Large masses of cancer tissue are removed to avoid excessive irradiation from injected gold. Repeated injections are safe and useful in areas not previously de-

stroyed. The volume of injected solution must be kept low and concentrated. Radiation therapy with radioactive gold avoids bladder and rectal complications so commonly seen with other types of radiation. Endocrine therapy has often given dramatic though temporary improvement and the relief of pain in some cases has been lasting. Castration followed by estrogen therapy is utilized only if pain occurs. Androgen therapy is used when extensive lesions do not benefit from administration of diethylstilbestrol.

Flocks, R. H.: Carcinoma of the prostate. J.A.M.A. 163:709-712, March 2, 1957.

Proctologic Office Procedures

About 90 per cent of rectal lesions can be diagnosed by digital and proctoscopic examinations. Passage of blood, pus, mucus, or other abnormal secretions; lower abdominal cramps; pain; protrusion; unexplained diarrhea; and increasing constipation necessitate proctologic study. Digital examination should be attempted before a proctoscope is inserted. If the index finger cannot be passed through the anal canal without pain, 4-per-cent cocaine in water-soluble jelly is applied. The finger is swept around the circumference of the bowel, and the perirectal tissues are palpated between the index finger and thumb. Proctoscopic examination generally can be performed without a preliminary enema. Cleansing may wash away evidence of disease. After the proctoscope is inserted, the instrument should be advanced under direct visualization with the obturator withdrawn. Undue force and overinflation with air must be avoided. After the proctoscope is passed through the anal sphincter, the lower sigmoid is the only area in a healthy individual that may be difficult to examine. If pain is severe, anesthesia is necessary. Precaution is particularly essential if anesthesia is used because rupture will not cause immediate symptoms. The proctoscope cannot be advanced 25 cm. in every instance.

Fansler, W. A.: Proctoscopy and proctologic office procedures. G.P. 15:101-106, Jan., 1957.

Cancer vs. Ulcer of the Stomach

The combination of neoplasm and ulceration in gastric lesions has been discussed by clinician and pathologist for many years. The incidence of malignant degeneration of benign peptic ulceration has been stated as from 0 to 100 per cent. The pendulum has swung periodically from one extreme to the other since 1845. Now the range is usually stated to be from 3 to 10 per cent, and many authorities hold that if there is any relationship between peptic ulcer and cancer it is the latter that causes the former rather than the reverse. Two cases of superficial spreading carcinoma with associated peptic ulceration are reported. One is living more than ten years and the other one year since operation. Serial block dissection is urged for all surgical specimens removed for gastric ulcerations so that such lesions are not missed. Also it is urged that all gastric resections for gastric ulceration include the regional lymph nodes and greater omentum despite the apparently benign gross appearance of the lesion.

Bralow, S. P., and Collins, M.: Relationship of peptic ulceration to superficial spreading carcinoma of the stomach. Gastroenterology 32:1152-1161, June, 1957.

Nuclear Size in Gastric Cancer

By a study of the gastric cytology of seventy-one patients, twenty-four asymptomatic normal controls, thirty-two proved pernicious anemia patients, fourteen patients with gastric cancer, and one with gastric cancer and pernicious anemia, it was determined that measurement of the size of the nuclei of gastric columnar cells is simple and reliable. These nuclei in patients with pernicious anemia are larger and more variable in size than are normal nuclei and the nuclei in patients with gastric cancer are still larger and more variable. This method of nuclear measurement by means of a micrometer eyepiece is useful as an adjunct in the diagnosis of malignant disease of the stomach.

Grable, E.; Zamcheck, N.; Jankelson, O., and Shipp, F.: Nuclear size of cells in normal stomachs, in gastric atrophy and in gastric cancer. Gastroenterology 32:1104-1112, June, 1957.

Book of Current Interest

THE YEAR BOOK OF CANCER. Compiled and edited by RANDOLPH LEE CLARK, JR., M.D., and RUSSELL W. CUMLEY, PH.D. Chicago. The Year Book Publishers, Inc. 1957. 572 pages. \$7.50.

Annual publication of "comprehensive abstracts of significant articles in the field of oncology, which have appeared during the preceding year" would be a laudable undertaking, but the excellence of this idea is not realized in the execution of *The Year Book of Cancer*.

It contains author-prepared abstracts of approximately 200 articles, 83 per cent of which appeared in 1955 and the remainder in the first three months of 1956.

Preparation of the abstracts by the authors of the articles would appear to have no advantage beyond minimizing the work of the compilers. It results in lack of uniformity of presentation and inequities of space allotment according to relative importance. Editorial participation is evident only in the short comments (average three lines) following half the abstracts and these are largely restatements of the authors' punch lines. The shortest editorial comment—"Quo vadis, domine?"—follows a report by Lewison, which might have been addressed more appropriately by the author to the editors.

More details of the mechanism of selection of articles abstracted, than those stated in the editors' introduction, would have been interesting. An editorial board of 119 "physicians and other medical scientists who have attained a somewhat more than usual acquaintance with the many aspects of the broad field of oncology" (40 Texans to 21 New Yorkers) were assigned to 25 sections—lung, skin, genetics, etc., each with a local section head, who apparently made the final selections for abstracting. Over-all assignment of section space seems disproportionate, considering Year Books are primarily for the general practitioner—female breast, 5 abstracts, 14 pages; radiotherapy, 11 abstracts, 29 pages; basic research, 16 abstracts, 37 pages.

Among the curios of selection is the sole foreign-language article—Lederman's report at the 1952 meeting of the

American Cancer Society, originally published (in English) in *J. Laryng. & Otol.*, June, 1954, and in French, with source acknowledgment, in *Ann. oto-laryng.*, No. 7, 1955—scant justification for the claim of covering "the world's foremost medicoscientific literature" appearing "during the preceding year."

Sixty-one (11 foreign) of the 500 journals scanned are represented, *Cancer* leading with 24 articles. Two articles from *CA—Bull. Cancer Progr.*, one carrying two extraneous illustrations, are credited to *Cancer*. Unconventional bibliographic citation reflects local practice.

The reason for special handling of the psychologic aspects by five original papers in full (24 pages) is not apparent.

General editing leaves much to be desired. Academic degrees are recorded unconventionally—bachelor and master degrees are listed along with, and sometimes after, the inclusive doctorate degree. Dr. Badger is given a gratuitous H. M. S., presumably Harvard Medical School.

Scarcely a page is free from inconsistencies and errors of careless and inexperienced editing, proof-reading, and technical production—the usual errors of medical journalism, "surgery" for operation, "malignancy" and "neoplasias" for malignant tumors, data, criteria, media, intima, etc., used indiscriminately as singular or plural; meaningless references and numbers carried over from the original articles; asterisks that lead nowhere; words omitted and words misused; incomprehensible constructions; and numerous errors of grammar, spelling, punctuation, and indexing.

In spite of the minor faults of this first so ambitious a volume, it represents a fair cross-section of the cancer literature of two to three years ago. It is neatly bound in red. No doubt the second volume, now in preparation, will make a more appropriate classroom exhibit on medical journalism.



a glance . . .

one-minute abstracts
of the current literature
on breast cancer . . .

Breast Cancer—Hormone Therapy

Six major measures are involved in the hormone therapy of breast cancer: (1) ovarian suppression, (2) adrenal suppression, (3) pituitary suppression, (4) androgen administration, (5) estrogen administration, and (6) adrenocorticoid administration. Castration is the primary measure for advanced breast cancer in the premenopausal woman. Regression of metastases following this procedure shows the tumor to be hormone-dependent. When exacerbation occurs, hypophysectomy is indicated. Further progress of the process indicates the administration of androgens. Bilateral adrenalectomy appears to have no role at present since more satisfactory improvement follows hypophysectomy and the patient can be more easily controlled. Inoperable breast cancer in the postmenopausal woman is best treated with estrogens. Those with only osseous lesions respond better to androgens. Exacerbation following androgen or estrogen therapy indicates hypophysectomy which will probably give another remission. Maximum survival of the patient with advanced breast cancer can be obtained by judicious use of the several procedures of hormonal therapy.

Kennedy, B. J.: The present status of hormone therapy in advanced breast cancer. Radiology 69:330-340, Sept., 1957.

Controversies in Breast Cancer

Among the differences of opinion concerning breast cancer are the following: (1) Is treatment worthwhile? (2) What is the choice between conventional radical mastectomy and superradical mastectomy, including supraclavicular, mediastinal, or other areas of spread? (3) Is simple mastectomy plus postoperative radiation effective? (4) Is castration indicated in absence of metastases? (5) Should the patient be treated during pregnancy or lactation? (6) How should metastatic carcinoma be treated? Debunking is a popular pastime in the medical as well as the lay literature and therapeutic defeatism is the fashion. The recent fatalistic attitude toward carcinoma of the breast should be a major concern of the medical profession. The authors present statistical data to show definite increase in longevity of treated breast-cancer patients compared with untreated patients. Five-year survival without treatment is approximately 20 per cent and with treatment, 50 per cent. The authors feel that the conventional radical mastectomy should be the accepted method of treatment except in those centers actively investigating possible improvements in therapy. Castration should be reserved for symptomatic therapy of metastatic disease, when indicated. Estrogen stimulation associated with con-

tinuation of pregnancy may adversely affect the growth rate of tumor cells. But each case must be handled on its own merits, considering the stage of the disease at the time of treatment, the desire for a child, and the health of the mother at the time pregnancy is detected. Among the modalities used in treatment of metastatic cancer of the breast are: hormone therapy including androgens, estrogens, and cortisone; radiation in controlling recurrences in the chest wall, limited bone metastases, and so forth; and radioactive gold in reducing pleural and ascitic effusions. The most difficult problem for the patient dying of carcinoma is the feeling of hopelessness, and too often this is fortified by her own physician. The psychological benefits gained from an optimistic attitude and active treatment cannot be overemphasized. The effectiveness of all palliative therapy will depend to a very large extent on the attitude of the physician.

Harrison, R. C.; Stanley, A. A. W.; MacGregor, D. J., and Fahey, J.: *Carcinoma of the breast; some controversial aspects.* *Canad. M. A. J.* 77:610-614, Sept. 15, 1957.

Hypophysectomy for Breast Cancer

Hypophysectomy achieves complete sex-hormone control by eliminating gonadotropic and adrenocorticotrophic hormones, and dispenses with the other pituitary hormones associated with breast cancer or prostatic cancer. Pituitary ablation has induced remissions for as long as thirty-two months in patients with metastatic cancer of the breast. Pituitary excision is not advisable for patients with disease in the liver or the brain. In postmenopausal women, chances of remissions are less the longer the duration of the postmenopausal state, and patients older than sixty years are seldom benefited by the operation. Failure to respond to androgen or estrogen therapy, however, does not mean that the patient will not benefit from hypophysectomy. Since 1951 a total of seventy-five patients with far-advanced cancer have had hypophysectomy; fifty-two were women with breast cancer who had not previously had their adrenal

glands removed. Results were evaluated in forty-one patients. Twenty-two (54 per cent) showed objective improvement with regression of metastases to bones, lungs, pleura, lymph nodes, and skin.

Luft, R., and Olivecrona, H.: *Hypophysectomy in the management of neoplastic disease.* *Bull. N. Y. Acad. Med.* 33:5-16, Jan., 1957.

Breast Cancer

Until recently cancer of the breast was thought of as a disease of autonomous growth and uniform progress, in which early diagnosis and prompt treatment by a standardized technique were the sole keys to success. But now it is recognized that many "early" cases have already transgressed the borderline of curability, that the real, overall cure rate in the best clinics is about 50 per cent, and that radiotherapy offers results which are little, if any, better than those from surgery. A ray of hope lies in endocrine therapy, which is now justified only in cases unsuitable for surgery or radiotherapy. It is unfortunate that early cancer of the breast is symptomless. Unlike many internal growths, there is no pain, hemorrhage, obstruction, or cachexia and it may not be noticed until too late. With the single exception of the multiple, tender nodules in both breasts in a young woman, every lump in the breast should be regarded as malignant until proved otherwise by microscopic examination. Disadvantages of the radical Halsted operation include sacrifice of an unnecessarily large part of the pectoral muscles, and scarring across the axilla, limiting abduction of the arm. This operation often fails in its purpose owing to involvement of the mediastinal lymph nodes. Theoretically, simple mastectomy should be sufficient where the disease is limited to the breast. When the disease has progressed further even radical mastectomy is generally insufficient. However, only the radical operation can offer a cure and remains the procedure of choice. McWhirter in Edinburgh, for the past fifteen years, has obtained results at least as good as can be obtained by orthodox methods, by following simple mastectomy with radiation from powerful

apparatus—a method not suitable for general use. Radiation is used generally after radical operations to destroy cancer cells left in the wound area and in the supraclavicular area, in cases not suitable for surgery, for local recurrences in skin, axilla, and supraclavicular region, and occasionally for distant recurrences, to control pain or to prevent ulceration. Endocrine therapy in cancer of the breast includes oophorectomy, administration of androgens and estrogens, adrenalectomy (with cortisone compensation), and hypophysectomy by surgery or by radiation with implanted radioactive yttrium—still in the experimental stage and attended by risk of damage to the optic nerve.

Illingworth, C. F. W.: *Cancer of the breast. Brit. J. Clin. Pract.* 11:21-23, Jan., 1957.

Synergistic Treatment of Breast Cancer

At Memorial Hospital, New York, a program was instituted more than four years ago to determine the relative benefits and possible synergism of combined hormone and radiation therapy, as compared with either alone, in the treatment of inoperable, recurrent, and metastatic breast cancer. A review of the literature shows that patients with metastases from breast cancer treated with radiation live longer than those untreated (twenty months as against eight months in one series of eighty-three cases). With hormone therapy it is reported that patients who respond live about twice as long as those who do not respond. In the present series of fifty-eight cases, those patients with inoperable disease localized to the breast and regional nodes or with one single metastatic site were treated by irradiation, while those with more advanced or widespread disease were treated both by radiation and with steroids. Whenever possible, patients with bilateral comparable disease were sought out, so that one side could be treated by both methods, leaving the lesions on the other side treated with hormones alone for comparison. Patients less than ten years postmenopausal received androgens, and older pa-

tients, estrogens for so long as regression was maintained or no progression occurred. Radiation therapy is an effective palliative in primary carcinoma of the breast and its metastases, the percentage improvement of individual lesions being higher than with steroids alone. The addition of steroid therapy did not appear to detract from or to enhance the radiation response; the effect of combined therapy was comparable to that of irradiation alone. The survival rates in comparable groups treated by combined therapy and with hormones alone showed no significant difference. In patients with widespread metastases in whom steroid therapy is indicated, additional irradiation is advisable for the prompt and effective control of individual lesions, such as bone metastases or ulcerating neoplasms.

Chu, F. C. H.; Sved, D. W.; Escher, G. C.; Nickson, J. J., and Phillips, R.: *Management of advanced breast carcinoma; with special reference to combined radiation and hormone therapy. Am. J. Roentgenol.* 77:438-447, March, 1957.

Hormone Therapy in Breast Cancer

At the Toronto General Hospital 330 patients with cancer of the breast have been treated with androgens, estrogens, or both since 1940. Results of treatment are compared with Shimkin's series of untreated cases in which the five-year survival rate was 20 per cent, and with Greenwood's untreated series in which the mean total survival period was thirty-eight months. Hormone therapy appreciably prolonged the survival of patients developing metastases. Response to hormone therapy is better when no previous treatment has been given. Percentage of response and length of remissions were greater from estrogens than from androgens in this series. Responses to the two were equal in postmenopausal women. Response to testosterone should be determined before the irreversible procedure of castration is performed. For osseous metastases, androgens and estrogens are both effective, but response to estrogens is more prolonged. Estrogen is to be preferred to androgen in lung metastases. Soft-tissue metastases respond more often to estrogen than to androgen, but androgen-induced

responses are for longer periods. In generalized disease estrogen gave a higher response rate but lengths of remissions were equal for estrogen and androgen. Mean survival after androgen therapy was ten months and eleven and a half months after estrogen therapy. If a short trial of testosterone therapy causes an exacerbation of the disease in premenopausal women, estrogen therapy should be instituted. Approximately 77 per cent of the patients in this series responded objectively or subjectively to hormone therapy. The five-year survival rate of the series was 30 per cent (untreated 20 per cent), and the average survival was eleven and a half months longer than for untreated recurrences. Compared with untreated patients with metastatic cancer of the breast, those treated with hormones live approximately one year longer, and three, compared with two, out of ten live more than five years.

Peters, M. V.: The influence of hormone therapy on metastatic mammary carcinoma. Surg., Gynec. & Obst. 102:545-552, May, 1956.

Breast Cancer—Choice of Therapy

A statistical study of breast cancer treated by two different methods at Confederate Memorial Center is presented. Ninety-eight cases of cancer of the breast in Stages I and II were treated by irradiation followed by simple mastectomy (not to be confused with McWhorter's recommended procedure of simple mastectomy followed by more powerful irradiation). One hundred and eighty-nine cases were treated by conventional radical mastectomy. The corrected five-year survival rate in the first group (98) was 33.8 per cent and in the second (189), 60.5 per cent. Local recurrences followed 10.9 per cent of 207 radical mastectomies, comparing favorably with other reported series. The higher five-year survival following excisional biopsy before radical mastectomy probably reflects a smaller and earlier primary lesion lending itself more readily to complete excision. In addition to type of treatment, the following factors affect the prognosis: age of patient,

heredity, location of tumor, endocrinological status of patient, biologic activity of tumor, host resistance, and delay in treatment.

Abramson, P. D.; Clifton, R. B., and Slagle, G. W.: Cancer of the breast; a comparison of two methods of treatment. Surgery 42:689-692, Oct., 1957.

Prognosis in Breast Cancer

At the Louisville (Ky.) General Hospital, the five-year survival rate of patients with breast cancer has doubled in the period, 1934 to 1951. The number of patients admitted, for diagnosis and treatment, more than six months after onset of the first symptoms in the first half of this period (1934 to 1944) was double that in the second half (1945 to 1951). Since there was no essential change in selection or treatment, the authors could find no reason for the improved survival rates except the decrease in the patient's delay in seeking medical care. Stage-I admissions are increased by this reduced patient delay, thus markedly influencing the end-results. Not knowing the precise time-growth pattern of any given tumor in the beginning, we must, as practical physicians, pursue early diagnosis to its limits. The idea that delay in diagnosis and treatment of carcinoma of the breast is of little importance must be rejected. In discussion, one of the authors reported that study of the more recent admissions (1952 to 1955) showed the percentage of Stage-I cases to have tripled—12 per cent in the 1934 to 1944 group; 28 per cent, 1945 to 1951; and 34 per cent, 1952 to 1955. Two hundred sixty consecutive patients with carcinoma of the breast, covering an 18-year period (1934 through 1955) are analyzed in categories of: stage on admission, five-year survival, and delay in diagnosis.

Moore, C., and Shaw, H. W.: Carcinoma of the breast; extent of original disease related to end-results. A.M.A. Arch. Surg. 75:598-602; disc. 602-604, Oct., 1957.

Inflammatory Breast Cancer

Inflammatory (erysipeloid) carcinoma of the breast grows rapidly and is very invasive. The inflammatory manifestations

are induration, redness, local heat, pig-skin or orange-peel appearance, tenderness, and sometimes pain. The inflammation is largely due to invasion of the subdermal lymphatics and capillary congestion; bacterial infection is rarely a factor. Systemic symptoms are absent. Many surgeons consider the condition inoperable since operation may disseminate the cancer and hasten the end. In a group of 1774 patients treated for pathologically proved carcinoma of the breast, including one male, 2.6 per cent had the primary inflammatory type. The prognosis of the disease is always grave, although several five-year survivals have been reported. The great danger is that less serious inflammation will be treated without recognition of the malignant nature of the lesion.

Pratt, J. P.: *Inflammations of the nonlactating breast.* *Am. J. Obst. & Gynec.* 74:844-850; disc. 850-851, Oct., 1957.

Breast Cancer

Analysis of the records of 1661 patients with cancer of the breast at the State University of Iowa Hospitals showed that the most important factor in failure to cure was the stage of the disease at the time of treatment. All other factors such as age, tumor size, hormonal pattern, type of treatment, socioeconomic status of the patient, and even delay of therapy due to either the doctor or the patient played minor roles compared with the stage of the disease. The overall five-year survival rate was 36.8 per cent. Of 913 patients treated by radical mastectomy, 46.8 per cent were living five years after diagnosis. The biologic behavior of the tumor and the factors of host resistance are important in a program stressing early diagnosis and treatment.

Hickey, R. C.: *Cancer of the breast; 1,661 patients.* *Am. J. Roentgenol.* 77:421-430, March, 1957.

Endocrines and Breast Cancer

At a conference on the endocrine aspects of breast cancer in Glasgow in July 1957, Cade (London) reported a series of 170 adrenalectomies for disseminated

breast cancer. The disease was controlled in 60 per cent of these cases. Age of the patient and histological type of the lesion had no effect on response to adrenalectomy. Hormone dependency could be predicted in a few cases by prior hormone therapy. Hellström (Stockholm) obtained remissions in 51 per cent of a group of 162 bilateral adrenalectomies. Remissions after operation were dependent solely upon the stage of the lesion at the time of operation. Atkins (London) found no superiority of response to either adrenalectomy or hypophysectomy in a series of sixty patients. Forrest (Glasgow) reported that necrosis of the pituitary by implanting yttrium-90 gives results comparable to those from hypophysectomy. There were no serious optical complications. Nabarro (London) obtained clinical remissions in six of twelve patients by pituitary-stalk section. Jessiman (Boston) found more than 80 per cent of mammary cancers to be hormone dependent and that this dependency persists to the terminal stages of the disease.

Anon.: *Endocrine aspects of breast cancer.* [Conferences.] *Lancet* 2:140-141, July 20, 1957.

Postadrenalectomy Danger

Increasing numbers of people have no adrenal gland and must depend on continuing doses of cortisone or its equivalent. In addition to patients with Addison's disease are those whose adrenals have been removed for Cushing's syndrome, cancer, diabetes, or malignant hypertension. Withdrawal of cortisone therapy in these patients is followed rapidly by addisonian crisis and death. Withdrawal may be caused unwittingly when the patient, for some intercurrent condition, vomits his cortisone tablets and no one thinks to replace them by injections. Or the patient may meet with an accident, come under new medical care and forget to explain his need. Or, even if he does maintain that he must continue his tablets, a ward nurse may take them from him, remonstrating: "The doctor will order anything you need." The doctor may be long delayed, or inexperienced, and may

not develop the need for cortisone on the first visit. It is recommended that patients on cortisone, like those on insulin, carry cards explaining their need, and that all nurses and others in charge of patients with deficient or absent adrenals be warned against this danger of sudden crisis and death.

Greene, R.: Dangers to the patient without adrenals. [Letters to the Editor.] Lancet 2:293, Aug. 10, 1957.

Breast Cancer—Early Diagnosis

The five-year survival rate of patients with breast cancer treated by radical mastectomy has doubled since Halsted's first report in 1907. This is largely due to earlier diagnosis and treatment. Cure rates and survival rates in breast cancer can still be materially increased by operating upon the doubtful or clinically benign lesion. About one in five ward patients are admitted with cancers in a stage in which diagnosis is either questionable or not cancer. End results can be improved by investigating rather than by observing such cases. Any dominant mass in the breast, even with benign appearance, should be excised for pathological examination. A significant number will prove to be early cancers. Such lesions have a better prognosis after early adequate treatment than the average clinically apparent breast cancer. If in doubt, take it out!

Urban, J. A.: Early diagnosis of breast cancer; salvage data with lesions considered clinically benign or doubtful prior to operation. Cancer 9:1173-1176, Nov.-Dec., 1956.

Value of Unsuccessful Therapy of Breast Cancer

The three principal therapeutic procedures in carcinoma of the breast are radical mastectomy alone, radical mastectomy combined with radiotherapy, and simple mastectomy with postoperative radiotherapy. For comparable series, five-year survival rates are 40 to 50 per cent, with no significant differences from the three procedures. Survival rates are increasing, showing that treatment is constantly improving in effectiveness. Local control or eradication of breast cancer by

either surgical or radiological means may not effect cure or influence survival, but failure to achieve local control means failure to cure. When the first recurrence is in a distant site or when the patient dies of cancer with no recurrence in the treated area, it may be assumed that the metastases occurred prior to treatment. The most direct evidence of the efficacy of treatment is offered by these uncured patients. Analyses of cure rates and survival rates obscure the values of different therapeutic techniques. Cure rates and survival rates indicate only that 40 to 50 per cent of breast cancers either grow locally and can be completely removed or grow so slowly that recurrence does not become manifest in less than five years.

Collins, V. P.: Breast cancer: the influence of treatment that fails to cure. Cancer 9:1177-1181, Nov.-Dec., 1956.

Inflammatory Breast Cancer

Thirteen cases of primary and five cases of secondary inflammatory carcinoma of the breast are reported. Adrenalectomy and oöphorectomy gave regressions in two of three cases in the primary group. One of these is surviving 29 months without progression of the disease. The remaining eight primary cases were treated by radical mastectomy and irradiation. Their average survival was 7.1 months. The five secondary cases were treated by adrenalectomy which gave objective remissions in three cases. One remission lasted three years and six months. Inflammatory carcinoma of the breast is a very virulent type with invariably grave prognosis. Radical mastectomy not only fails to cure but is actually deleterious as it is often followed by prompt local recurrence, generalized metastases, and early death. Irradiation is equally ineffective.

Dao, T. L., and McCarthy, J. D.: Treatment of inflammatory carcinoma of the breast. Surg., Gynec. & Obst. 105:289-294, Sept., 1957.

Mammary Cancer

The following points concerning cancer of the breast were reported at an international symposium in Perugia in July, 1957. Oettlé and Higginson stated that the

incidence of cancer of the breast among the Bantus in Johannesburg is lower in all age groups than in Denmark or the United States. Most Bantu women start child-bearing at age fifteen and bear many children. The incidence of breast cancer is higher among those women who started to have children late. Although gynecomastia is common in young Bantus, the incidence of cancer of the male breast parallels that in the United States. Bucalossi and Veronesi (Milan) found, in a survey of four thousand patients, a high, familial incidence of breast cancer but no evidence of transmission of a tumor agent from mother to daughter. They also reported that menopause is earlier in breast-cancer patients. Laman and Rezek (Miami) used massive doses of testosterone (100 gm.) and claimed that side effects are thus abolished. Better results were obtained by massive doses of hormones than by any form of endocrine ablation.

Anon.: Mammary cancer. [Congresses.] Lancet 2:289, Aug. 10, 1957.

Co⁶⁰ in Breast-Cancer Radiotherapy

Teletherapy with cobalt-60 has superseded 200-kv. roentgen rays in general radiotherapeutic practice. The cobalt-60 teletherapy unit is able to concentrate sources up to 3000 curies in a disk of 2-cm. diameter. Skin tolerance is greater with radioactive cobalt. Since doses of 6000 to 7000 r in six weeks produce only slight erythema and pigmentation, skin

reactions are not deterrents to treatment. Radiation sickness is less likely with Co⁶⁰, probably because scattering of radiation is less than with roentgen rays. Because of increased depth dose, decreased bone absorption, and better skin tolerance, treatment procedure is simplified. Fewer fields are needed, and cumbersome rotation therapy is unnecessary. The number of fields required depends on the accessibility and proximity of the tumor to the surface. Protection from deeply penetrating and ever-present radiation must be constant. Cobalt-60 radiation cannot be turned on or off but must be shielded by thicknesses of heavy metal. Greater protection of uninvolved vital structures is required with Co⁶⁰ therapy than with 200-kv. roentgen rays. With roentgen-ray therapy, skin reaction may be used as a warning against overdosage, but known limits of radiation tolerance must be observed with cobalt-60. The radiotherapeutic problem in breast cancer is with the regional lymph nodes and distant metastases. Postoperative radiation therapy is directed to the lymph nodes at the apex of the axilla, in the supraclavicular fossa, and along the internal mammary vessels. The choice between roentgen-ray and cobalt therapy of metastases in bone, skin, lungs, and other viscera depends on the size of the required dose and on the possible reactions such a dose would produce.

Silverstone, S. M., and Simon, N.: The advantages of cobalt-60 in the practice of radiotherapy. J. Mount Sinai Hosp., New York 24:124-136, March-April, 1957.

Book of Current Interest

CANCER. Edited by RONALD W. RAVEN. Vol. I. London. Butterworth & Co., Ltd. 1957. 539 pages. \$12.00.

First of six volumes in eleven parts, and index, covering authoritatively practically all aspects of cancer except surgical details. Titles of the parts are: research into causation, pathology of malignant tumors, additional pathological aspects, geography of cancer, occupational cancer, cancer education, cancer detection, clinical aspects,

radiotherapy, chemotherapy, and public health aspects of cancer. Some of the contributions—all by internationally known specialists—are of nearly 100-page length and all carry comprehensive bibliographies. If this first volume is representative, the completed work will be the best single source of current cancer information.

Benign and Malignant Lesions of the Nipple

Joseph H. Farrow, M.D.

The nipple is a conic organ which gives outlet to the secretions of the mammary gland. It contains the lactiferous ducts and muscular tissue and is covered by thickened and wrinkled skin that is perforated by varying numbers of duct orifices. Because of its function and anatomic location the nipple plays an important role in the diagnosis of pathological lesions of the breast. Thus, the character of abnormal discharges from the duct orifices may be the clinical basis for detecting such lesions as intraductal papilloma, duct stasis, or cancer. Alterations of the nipple by ulceration or retraction are recognized features of breast carcinoma. On the other hand, the nipple may be the site of diseases and new growths which are not peculiar to the breasts.

The lesions of the nipple that are most common as well as most difficult to differentiate are Paget's disease and eczema. Paget's description of the disease which bears his name was published in 1874 under the title, "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland." It contained only 1050 words and has no equal for clarity and brevity in medical literature. A portion of this classic, which was published in the *St. Bartholomew's Hospital Reports*, London, 10:87-89, 1874, follows:

"The patients were all women, various in age from 40 to 60 or more years, having in common nothing remarkable but their disease. In all of them the disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of very acute diffuse eczema, or like that of an acute balanitis. From such a surface, on the whole or greater part of the nipple and areola, there

was always copious, clear, yellowish, viscid exudation. The sensations were commonly tingling, itching, and burning, but the malady was never attended by disturbance of the general health. I have not seen this form of eruption extend beyond the areola, and only once have seen it pass into a deeper ulceration of the skin after the manner of a rodent ulcer.

"In some of the cases the eruption has presented the characters of an ordinary chronic eczema, with minute vesications, succeeded by soft, moist, yellowish scabs or scales, and constant viscid exudation. In some it has been like psoriasis, dry, with a few white scales slowly desquamating; and in both these forms, especially in the psoriasis, I have seen the eruption spreading far beyond the areola in widening circles, or, with scattered blotches of redness, covering nearly the whole breast. I am not aware that in any of the cases which I have seen the eruption was different from what may be described as long persistent eczema, or psoriasis, or by some other name, in treatises on diseases of the skin; and I believe that such cases sometimes occur on the breast, and after many months' duration are cured, or pass by, and are not followed by any other disease. But it has happened that in every case which I have been able to watch, cancer of the mammary gland has followed within at the most two years, and usually within one year. The eruption has resisted all the treatment, both local and general, that has been used, and has continued even after the affected part of the skin has been involved in the cancerous disease."

It was entirely a clinical description and therefore contained no reference to the cells, subsequently called Paget's cells, which are a characteristic histological feature of this condition. Although there were controversial opinions for many years regarding both his observations of the clinical course of the disease and the

Breast Service, Memorial Hospital, New York, New York.

nature of the Paget's cells as described by others, this condition is now generally regarded and treated as a type of breast cancer. One feature which Paget did not mention is that it has been observed only as a unilateral disease.

Eczema is not uncommonly bilateral but may be unilateral. As a rule the onset is more acute than in Paget's disease and the condition appears in patients of a

younger age group. While eczema may resemble Paget's disease symptomatically and clinically, it may initially involve only the areola but later spread to the nipple, whereas Paget's disease first appears on the surface of the nipple.

An important point regarding the superficial lesions of the nipple is that they require a prompt biopsy for differential diagnosis and proper treatment.

Legends

(See pages 18 and 19.)

Fig. 1. Papillomatosis. Age 23. Crusting, bleeding, and itching left nipple for 1½ years. Lesion confined entirely to surface of the nipple without palpable induration or mass in the breast. Biopsy: Atypical papillomatosis of terminal ducts, cystic mastopathy.

Fig. 2. Sclerosing adenosis and duct papillomatosis. Age 52. Indolent, pruritic sore involving left nipple and areola for 2 years. Recurrence following limited excision 1 year previously. Biopsy: Ulcerative fibrosis and inflammation. Did not heal following antibiotic therapy and hot soaks. Wide excision. Pathological report: Sclerosing adenosis and duct papillomatosis.

Fig. 3. Eczema. Age 28. Three weeks' duration of itching, scaly lesions involving the nipples and areola of both breasts. Examination revealed bilateral involvement of the nipples and areolas by a dry, scaly eczematoid dermatitis. No mass palpable in the breasts. Unfortunately a biopsy was not done because the patient was referred for immediate dermatological therapy due to the acute onset of the condition and the bilateral involvement.

Fig. 4. Eczema. Age 55. Itching of left nipple for 2 months. Progressive, scaly erythema of skin and adjacent base of nipple of 2 weeks' duration. Superficial lesion without underlying induration or mass in the breast. Biopsy: Eczema. Referred for dermatological therapy.

Fig. 5. Syphilis. Age 22. Postpartum 4 months without nursing child. Four weeks' history of sticking pain in breast with rapid onset of raw, granular lesion involving the right nipple and areola. Biopsy: Granulation tissue, serodiagnosis requested. Repeated Mazzini, Kline and Kahn tests were 4 plus. Referred for antiluetic therapy.

Fig. 6. Eczema. Age 41. Eight months previously patient had noticed reddening of the right nipple and staining of her night clothes by a clear fluid. Applied ointments without relief. For 2 months pain in region of the nipple. The surface of the nipple and superior half of the areola was scaly with a leathery thickening of the skin, which cracked on palpation. A thin, serous exudate oozed from the fissures in the areola. Biopsy: Chronic inflammation consistent with eczematoid dermatitis. Referred for dermatological x-ray therapy.

Fig. 7. Melanoma. Age 50. Purulent discharge from right nipple for 3 months. Pigmented area on nipple present for as long as she could remember. It had become larger during the past month. Non-ulcerated, clinically benign, pigmented lesion 1.5 by 1 cm. in-

volving the nipple and adjacent areola. No axillary adenopathy. Local excision and simple mastectomy. Pathological report: Malignant melanoma of nipple. Breast tissue negative. Follow-up report 9½ years later indicated no evidence of disease.

Fig. 8. Cancer. Age 44. Painless retraction of nipple and progressive reddish induration of nipple and areola for one month. Examination revealed underlying mass that measured 1.5 cm. Biopsy: No evidence of Paget's disease but subepithelial area of mammary cancer. Radical mastectomy. Pathological report: Infiltrating duct carcinoma, Grade III, with metastases to axillary lymph node.

Fig. 9. Paget's disease. Age 68. Complaining of progressive red scaly lesion of the right nipple and areola for 3 weeks. Examination demonstrated a 4-cm., scaly, granular lesion involving the nipple, areola, and adjacent skin, and a well defined 7-cm. mass in the breast. Biopsy: Paget's disease. Radical mastectomy. Pathological report: Paget's disease, infiltrating duct cancer, Grade III, metastatic to other areas in the breast, and multiple axillary lymph nodes.

Fig. 10. Paget's disease. Age 37. Red, weeping, and tender right nipple and areola for 6 months. Entire nipple and a small margin of the areola were indurated, granular, and erythematous. No mass palpable in the breast. Biopsy: Everted, inflamed terminal duct. Repeat biopsy: Paget's disease. Radical mastectomy. Pathological report: Paget's disease with lobular, comedo and infiltrating duct carcinoma; axillary lymph nodes negative. Follow-up report 10 years later revealed no evidence of disease.

Fig. 11. Paget's disease. Age 58. Asymptomatic mass in the left breast for two months. Although patient had not noticed any alterations of the nipple, examination revealed a scaly erythema involving the nipple and adjacent areola. Underlying this area was an infiltrating 2.5 cm. mass with skin attachment. Biopsy: Paget's disease. Radical mastectomy. Pathological report: Paget's disease; infiltrating duct carcinoma with metastases to multiple axillary nodes. Patient died six years later with mediastinal metastases.

Fig. 12. Basal-cell epithelioma. Age 49. Ten years previously "soap burn" of right nipple. Had persisted without healing as a scaly and crusty lesion. No symptoms. Nipple indistinct due to scar and 2 discrete ulcerations, with well defined rolled edges, measuring 1.5 and 2 cm. respectively. No masses were felt in the breast. Biopsy and wide excision. Pathological report: Basal-cell epithelioma of nipple.

BENIGN



Figure 1. Papillomatosis.



Figure 2. Sclerosing adenosis and duct papillomatosis.



Figure 3. Eczema.

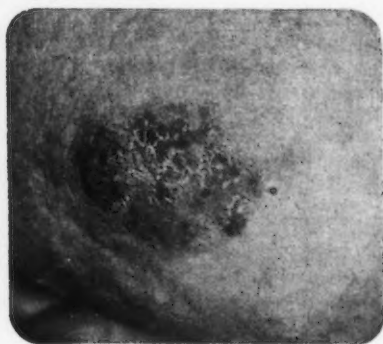


Figure 4. Eczema.



Figure 5. Syphilis.



Figure 6. Eczema.

F THE NIPPLE

MALIGNANT

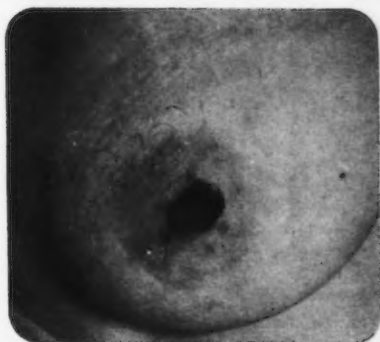


Figure 7. Melanoma.



Figure 8. Cancer.



Figure 9. Paget's disease.



Figure 10. Paget's disease.



Figure 11. Paget's disease.

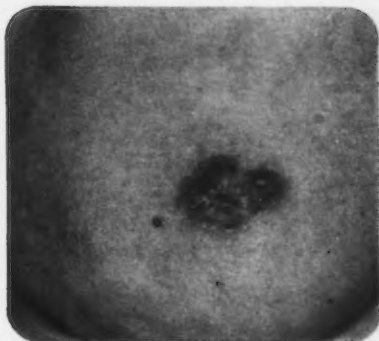


Figure 12. Basal-cell epithelioma.

Radical Mastectomy with en Bloc in Continuity Resection of the Internal Mammary Lymph-Node Chain

Jerome A. Urban, M.D.

The five-year salvage rate of primary operable breast cancer treated by radical mastectomy has doubled in the last fifty years. At present, most American clinics obtain a five-year salvage rate of about 55 per cent as compared with the 28.9 per cent five-year salvage rate reported by Halsted in 1907. Since the operative procedure has remained essentially unchanged we must attribute this improved salvage rate to earlier diagnosis which more frequently provides a patient free of systemic metastases at the time of primary treatment. Nevertheless, approximately 20,000 women die of breast cancer annually in the United States. Further improvement in the primary control of this disease will come most likely from a combination of early diagnosis (in the clinical sense—detecting the cancer when it has just recently produced signs and symptoms) and early, more adequate surgical excision of the cancer.

With the public more aware of the importance of cancer detection we are seeing a greater number of patients whose lesions have not as yet developed the clinical characteristics usually associated with breast cancer. Clinical diagnosis is becoming more difficult and reliance more frequent upon local excision of clinically benign lesions primarily to rule out cancer. A recent study covering some 1500 cases demonstrated that more than 10 per cent of clinically benign lesions were proved to be carcinoma following local excision and frozen-section examination. These same clinically benign lesions showed a much better five-year salvage rate following radical mastectomy (74 per

cent) than did the cancers which were clinically apparent (only 49 per cent). Any dominant mass which persists in the breast should be excised for pathological examination even though it appears clinically benign. A significant number of these apparently benign lesions will prove to be early cancers, which have a better prognosis after early adequate treatment than the average clinically apparent case of breast cancer. In order to detect these early clinical cases the general medical man, who is usually the first to see these lesions, must maintain a constant suspicion of carcinoma toward any persistent mass in the breast.

The definitive surgical treatment of a cancer should consist of the en bloc excision of the primary tumor together with its primary lymph-node drainage depots before distant metastases have occurred. The classical radical mastectomy has often been cited as an ideal cancer operation since it includes removal of the primary lesion in continuity with its primary lymphatic drainage depot—the axillary nodes. Unfortunately, this assumption is only partially true since the lymphatic drainage of the breast extends into two main depots—the axillary and internal mammary lymph-node chains. From these depots secondary drainage extends mainly into the nodes at the base of the neck where the lymphatic vessels drain into the jugulo-subclavian venous junction. A significant number of breast cancers also spread through hematogenous routes which are not amenable to our present surgical therapy.

The axillary nodes represent the primary lymph-node complex most frequently involved with metastases. There is abun-

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INVASION OF INTERNAL MAMMARY LYMPH NODES
IN BREAST CANCER

		Inner half	Outer half	Total
All nodes	—	16	33	49
Axilla	+	12	40	52
Internal mammary	+	6	2	8
Both	+	27	14	41
		61	89	150 cases

(Handley and Thackeray, 1954)

Table 1.

dant proof to show that the next most frequently involved regional lymph-node group is the internal mammary chain of nodes. Approximately 20 to 35 per cent of all operable breast cancers show metastases in the internal mammary nodes as compared with 40 to 60 per cent with axillary-node metastases. Handley, in England, demonstrated through biopsy of the internal mammary nodes at the time of radical mastectomy that 49 of 150 consecutive operable breast cancers showed internal mammary-node metastases as compared with 93 with axillary-node metastases. Dahl-Iversen, in Denmark, operating on early clinical breast cancers showed that 41 of 100 consecutive cases had positive axillary nodes, 17 had positive internal mammary nodes, while only three had positive supraclavicular nodes. In 8 per cent of his cases only the internal mammary nodes were involved.

Since the internal mammary chain of nodes is a primary drainage depot of the breast frequently involved with metastases the most logical step in extending the surgical attack on primary operable breast cancer is to combine the en bloc resection of this nodal complex together with the radical mastectomy procedure. In 1951 we devised an original operative technique—"Radical Mastectomy with En Bloc in Continuity Resection of the Internal Mammary Lymph-Node Chain"—in order to remove the primary lesion together with both of its primary lymph-node drainage depots. Since then we have performed this procedure in more than 285

cases of operable breast cancer. A practical technique which resulted in minimal deformity, good functional result and no increase in mortality has been developed. This procedure has been applied mainly to subareolar and medial half lesions since they frequently metastasize to the internal mammary nodes early in the course of the disease.

The operative technique has been presented in detail elsewhere.¹ In brief, the full thickness of that portion of the chest wall which includes the ipsilateral internal mammary lymph-node chain extending from the first rib to the sixth rib and from the midline of the sternum to the costochondral junctions is resected en bloc in continuity with the classical radical mastectomy procedure. All the salient features of the classical radical mastectomy, such as wide skin excision, meticulous dissection of the axilla, thin skin flaps, and en bloc resection are maintained, and to this is added the en bloc resection of the internal mammary lymph-node chain. The



Fig. 1. Primary lymphatic drainage of the breast. Insert, incision used for upper, inner quadrant lesions.

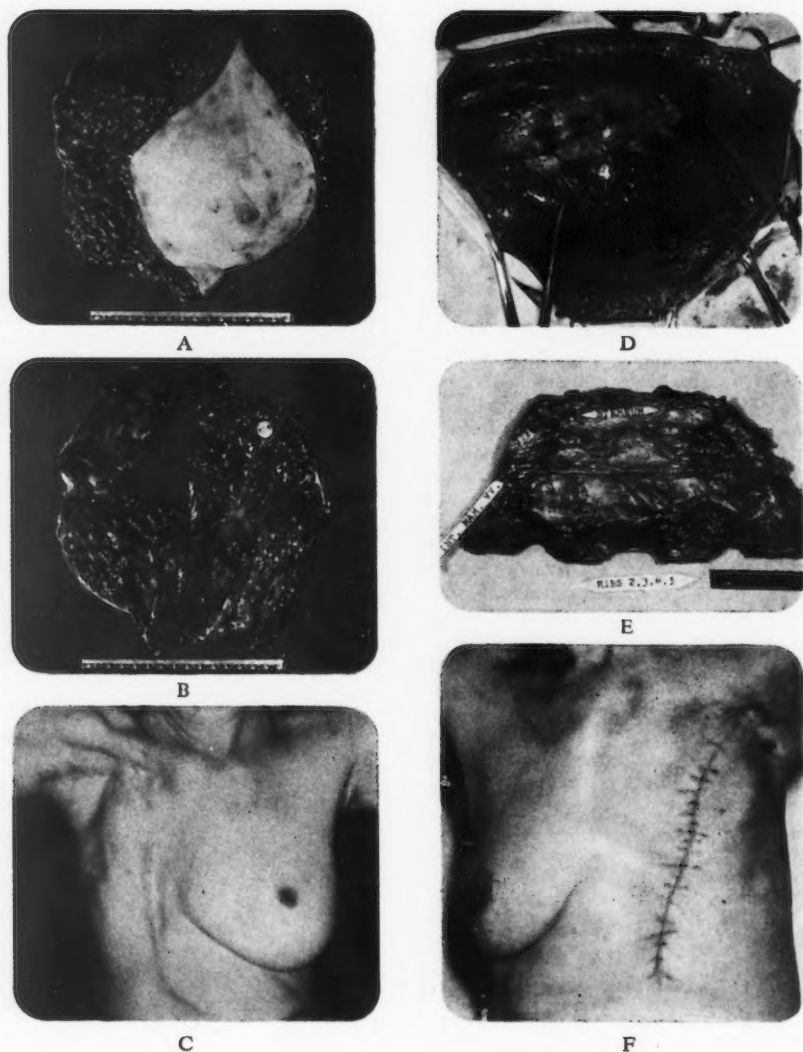


Fig. 2. A & B. Specimen demonstrating wide skin excision and relationship of resected portion of chest wall to the overlying muscle and breast. C, Postoperative appearance of patient. D, Operative field—note thin skin flaps, clean axilla, tense fascial closure of chest wall. E, Resected portion of chest wall—parietal pleura removed to show large metastatic nodes on sternal side of internal mammary vessels. F, Postoperative appearance of patient.

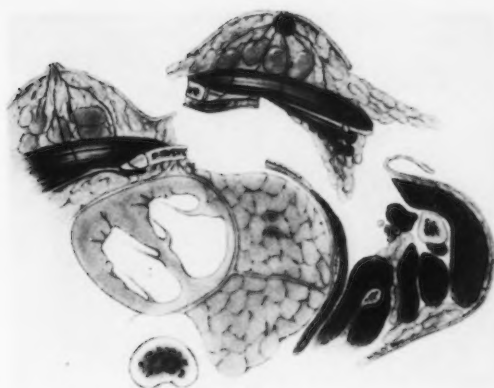


Fig. 3. Operative specimen showing the relationships among the primary lesion, the lymphatic vessels draining the tumor, and the primary lymph-node depots draining the breast.

operative defect in the chest wall is repaired by an autogenous graft of fascia lata sewn in place flush with the outer surface of the chest wall under maximum tension—affording adequate support and eliminating or minimizing paradoxical motion. In some 50 instances we have repaired the chest-wall defect satisfactorily with homograft fascia lata. Primary closure of the wound is usually obtained through mobilization and fixation of the skin flaps.

This more extensive procedure should be carried out only under ideal conditions by competent surgeons with the assistance of an excellent anesthesiologist and with adequate postoperative care in order to avoid undue postoperative mortality and morbidity. It should be applied to patients in good general condition in whom one has reason to believe that the disease has not progressed beyond the regional lymphatics. We have found that a significant number of operable cases have their disease confined to the breast and either the internal mammary nodes or the axillary nodes without systemic spread at the time of operation to warrant more extensive surgical approach. When done under ideal conditions this operation has not caused any appreciable interference with the patient's normal activities. It is a practical procedure necessitating hospitalization for only seven or eight days postoperatively.

In our practice we have not given postoperative roentgen-ray therapy except to those cases in which positive nodes were

found in either the apex of the axilla or in the first interspace of the internal mammary chain. In these cases because of the likelihood of further extension of disease into the base of the neck deep x-ray therapy has been administered to the base of the neck through an anterior and posterior port extending from the lower border of the first rib upward. Each port receives 300 r (in air) $\times 10$ for a total dose of 3000 r (in air) of the usual 250 kv. high-voltage therapy administered over a period of four weeks. No x-ray therapy is administered to the chest wall itself. By concentrating x-radiation therapy to the base of the neck a high tumor dose can be delivered safely to this area without causing excessive systemic reaction and pulmonary fibrosis.

Operative Findings and Results

This operative procedure was used in 285 patients ranging from 30 to 70 years of age at Memorial Center in New York City with less than 1 per cent postoperative mortality. Neither of the two postoperative deaths was directly attributable to the operative procedure. One occurred following a cerebrovascular thrombosis, the other from a perforated peptic ulcer. There has been only slight immediate postoperative discomfort but no appreciable longstanding morbidity. With the support of the chest wall by fascia lata, little added deformity is apparent in most cases as compared with the classical radical mastec-

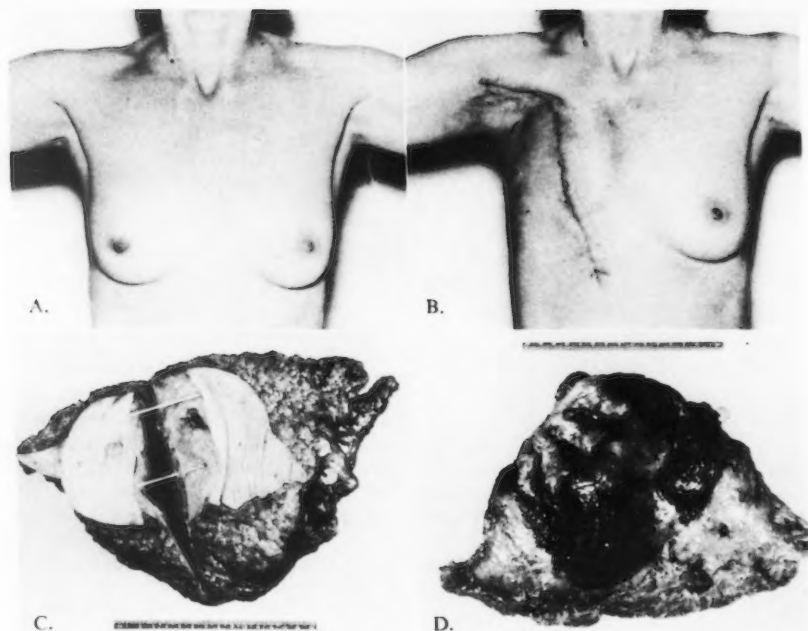


Fig. 4. A, Preoperative appearance. A tumor 1.5 cm. in diameter lies beneath the upper, outer portion of the right areola. The axilla was clear at examination. B, Postoperative appearance. This patient had an infiltrating duct carcinoma, Grade III, beneath the right areola. One metastatic node 6 mm. in diameter was found in the lower portion of the axilla. One involved node, 3 mm. in diameter was noted in the third intercostal space of the internal mammary chain. Patient is now clinically free of disease six years postoperatively—with perfect function and no paradoxical motion. She has had no x-ray therapy. C, External aspect of operative specimen showing adequate skin margins and wide dissection. D, Internal aspect of operative specimen (after removal of the soft parts of the chest-wall resection in the pathology laboratory). The bony structures of the chest-wall resection including a portion of the sternum, and the second, third, fourth, and fifth costal cartilages are still attached to the overlying pectoralis major muscle.

tomy result. Of the first 270 cases analyzed 35.5 per cent showed positive internal mammary nodes and 48.2 per cent had positive axillary nodes. Of the cases with negative axillae, 15 per cent had positive internal mammary nodes. In almost 8 per cent of the cases only the internal mammary nodes showed involvement. If this group of patients had been treated by the classical radical mastectomy procedure 35.5 per cent of them would have harbored gross metastatic disease in a regional lymph node postoperatively.

When the axillary nodes were positive 58 per cent of the overall group showed

internal mammary-node metastases. This incidence rose to 60 per cent in the medial lesions and fell to 50 per cent in the lateral lesions. When the axillary nodes were negative, the internal mammary nodes were positive in 15 per cent of the overall group. This was slightly higher for lesions of the medial half and fell to a 12 per cent incidence for lesions of the lateral half. When the primary tumor presented in the extreme upper inner quadrant of the breast, a greater number of patients had internal mammary-node metastases than had involvement in the axilla. It is interesting that all of our cases

28 CASES
INTERNAL MAMMARY NODES POSITIVE
AXILLARY NODES NEGATIVE

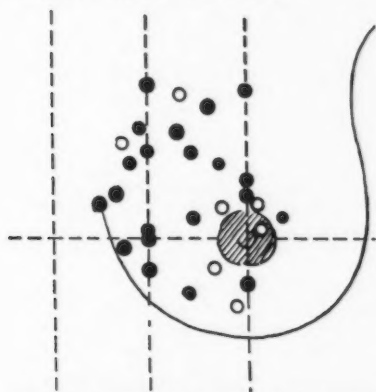


Fig. 5. Plotting the location of the primary lesions in which internal mammary-node metastases were present while the axillary nodes were clear. (Open circles represent cases of Dr. Everett Sugarbaker—solid circles represent our own group.)

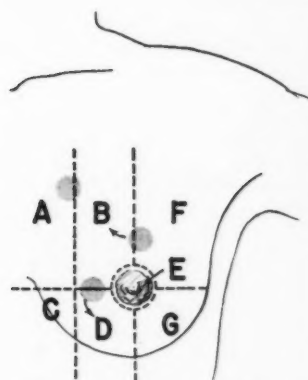
in which the primary tumor presented beneath the areola or nipple showed negative internal mammary nodes when the axilla was negative. However, when the axilla was involved 60 per cent of these

cases showed positive internal mammary nodes. (Most of the lateral lesions in this series were located close to the midline of the breast—as a rule we have not applied this technique to early lesions in the outer portion of the lateral half of the breast.)

The highest incidence of metastatic nodes in the internal mammary chain appeared in the second interspace, then in the third, and finally in the first interspace, and in that order. The fourth interspace was relatively infrequently involved and in only five cases did we find positive nodes in the fifth interspace. In evaluating 95 cases with positive internal mammary nodes there is a slightly higher incidence of involvement in the nodes lying between the internal mammary blood vessels and the sternum as compared with the nodes lying laterally to these vessels.

At present 55 patients have undergone this procedure more than five years ago. In this group of patients with a 40 per cent incidence of internal mammary-node metastases and a 56.4 per cent involvement of the axillary nodes, we obtained a five-year survival rate of 65.4 per cent and a five-year survival rate clinically free of disease of 60 per cent. This is approximately 11 per cent greater than the salvage rate clinically free of disease (48.5

NODE METASTASES IN PRIMARY OPERABLE BREAST CANCERS
UNDERGOING COMBINED PROCEDURE



Location	A	B	C	D	E	F	G	TOTAL
Total number of cases	63	107	28	28	21	16	7	270-100%
All nodes clear	33	54	11	11	4	4	2	119-44%
Internal mammary only involved	7	8	3	2	0	1	0	21-7.8%
Axillary only invaded	5	22	6	6	7	6	3	55-20.4%
Both internal mammary and axillary invaded	18	23	8	9	10	5	2	75-27.8%
Overall Group	Cases 44% All nodes clear 35.5% Positive internal mammary 48.2% Positive axillary 7.8% Only positive internal mammary 15. % Cases with clear axilla had positive internal mammary							

Table 2. Lesions touching vertical lines are assigned to the sector lying medially to that line. Those touching the horizontal line are assigned to the sector below. Lesions lying behind the areola and nipple are assigned to Sector E.

per cent) that one would anticipate had similar material been treated by the classical radical mastectomy procedure. (This latter figure is obtained by projecting the 55 cases into the salvage rate of 1,000 primary operable breast cancers treated between 1944 and 1947 by radical mastectomy and postoperative x-ray therapy at the Memorial Center—the salvage rate being calculated for each sector of the breast and according to axillary-node involvement.) Of 22 patients with positive internal mammary nodes eight are free of disease more than five years postoperatively and two others are living with systemic metastases but without local disease. Of the patients with axillary node involvement in this group of patients 48 per cent are free of disease five years postoperatively, 36.3 per cent of those with internal mammary involvement are free of disease, and 81 per cent of those with all nodes negative are free of disease five years postoperatively. Of the original 55 operated upon more than five years ago, 26 patients would have been considered categorically inoperable for radical mastectomy by some on the basis of either internal mammary-node involvement or involvement of the nodes in the apex of the axilla or both. In this group of 26 patients 38 per cent are now clinically free of disease and 46 per cent are surviving more than five years postoperatively.

Summary and Conclusions

1. We are convinced that a combination of early diagnosis and early more thorough surgical treatment will result in an increased salvage of patients with primary, operable breast cancer.

2. Radical mastectomy with en bloc in continuity resection of the internal mammary lymph-node chain extends the classical radical mastectomy procedure to include the other primary lymphatic drainage depot of the breast—the internal mammary chain. In our hands it has proved a practical procedure with no in-

Reference

1. Urban, J. A.: Radical mastectomy with en bloc in continuity resection of the internal mammary lymph node chain. *S. Clin. North America* 36: 1065-1082, 1956.

Primary Operable Breast Cancer COMBINED PROCEDURE - 5 YEAR SURVIVAL RATE				
55 Cases	Total Number	Alive free of disease	Alive with disease	5 Year Survival
All nodes clear	21	17	0	17
Only axilla invaded	12	8	1	9
Only int. mammary invaded	3	1 1 po death	0	1
Both axilla and int. mammary invaded	19	7	2	9
Entire group	55	33	3	36
40. % Pos. int. mammary	5yr. survival rate		65.4%	
56.4 % Pos. axilla	5yr. Clinically free of disease		60.0%	

Expected 5 yr. salvage rate (clinically free of disease) for similar material treated by radical mastectomy and post-operative x-ray therapy 48.5%

Table 3. Salvage rate of fifty-five consecutive primary operable breast cancers treated by the combined operation more than five years ago.

creased postoperative mortality (less than 1 per cent).

3. At present 285 patients with breast cancer have undergone this procedure. In the first 270 cases evaluated 35.5 per cent had internal mammary lymph-node metastases and 48.2 per cent showed axillary-node involvement. Of the cases with clear axillas, 15 per cent had internal mammary metastases.

4. An increased (60 per cent) five-year survival rate clinically free of disease has been obtained in the first 55 primary operable breast cancers undergoing this procedure as compared with the salvage rate of similar patients treated by radical mastectomy (48.5 per cent). Of 22 patients with positive internal mammary nodes eight are now free of disease between five and six years postoperatively. Only four local recurrences, as the first sign of recurrent disease, have been noted in the first 285 patients.

5. This procedure is indicated for Stage I and early Stage II cases, particularly when the primary tumor arises in the central and medial sectors of the breast. It cannot be expected to help the advanced case of breast cancer with subclinical systemic disease.

Precancerous Lesions of the Breast

Max Cutler, M.D.

Cancer of the breast is not only the most important of the major types of cancer, it is also one of the most treacherous. Fortunately, however, the disease lends itself to a reasonable degree of prevention and early diagnosis.

The most interesting and perhaps the most important phase of the problem of mammary cancer is related to the so-called precancerous lesions. Cystic disease of the breast, papillomata, and so-called Schimmelbusch's disease—commonly regarded as precancerous lesions—require clarification. An effort is made in this presentation to interpret the significance of these lesions and to indicate the proper course of treatment.

Clinical, pathological, and experimental data have accumulated which clearly indicate that cancer in general and cancer of the breast in particular are not sudden events or accidents in previously normal tissues. On the contrary, it would seem that as a rule cancer is the end-result of a series of changes which may have begun many years before. In the breast it has been possible to demonstrate a series of interrelated and consecutive tissue changes which progress slowly over a period of many years. Our evidence leads us to the opinion that mazoplasia is not a step in this pathological process, and that the first microscopic evidence of the changes that ultimately lead to cancer is the formation of microscopic cysts. The epithelial hyperplasia which leads to cyst formation may stop, and the breast may remain purely cystic throughout the life of the individual, but in a considerable proportion of cases the hyperplasia continues and sooner or later becomes complicated by the advent of the neoplastic process or the formation of papillomata. The combination of cysts and papillomata gives rise to a condition known as Schimmelbusch's disease. Again, a breast which is the site of Schimmel-

busch's disease may remain so throughout the lifetime of the individual, but in a considerable proportion of cases the epithelial change progresses, and at some point in this process epithelial cells invade outside boundaries and cancer is established.

The accumulated evidence suggests that cysts and papillomata are precancerous or potentially cancerous states. By these terms it is implied that if the epithelial changes associated with these conditions progress, cancer is the inevitable consequence. However, epithelial changes may regress at any point and disappear, or they may be arrested and remain stationary throughout the lifetime of the individual; but if they progress, carcinoma is finally established. "Precancerous" does not mean that these lesions inevitably become cancerous, but that they are potentially cancerous. It is also important to emphasize at this point that the events which have been described may occur with varying degrees of rapidity. Many of these changes require as long as thirty or even forty years to develop. At the other extreme, however, the process may be very rapid; in fact, it may be so rapid as to end in cancer without leaving any discernible trace of the previous stages through which it has passed. In such cases it is not absolutely certain whether cancer has arisen by this process or by another unknown method.

Cystic disease of the breast is usually diffuse and often bilateral. These facts were especially emphasized by Reclus, and the condition is now usually designated as Reclus' disease. In many instances one cyst outgrows its neighbors and reaches a sufficient size to be clinically palpable. In these larger cysts, the epithelium is usually so degenerated it fails to respond to stimuli, and for this reason cancer, rarely complicates the larger cysts. When cancer is discovered in the wall of a cyst it has usually originated in the active epithelium of a duct entering it and not in the degenerated epithelium which lines the cyst.

Surgical Staffs of Cedars of Lebanon and St. Johns Hospitals, Los Angeles, Calif.

It is not fully appreciated that when a cyst is clinically palpable as a single lesion it is almost invariably surrounded by numerous smaller cysts that are too small to be palpable. It should be noted also that microscopic cysts are potentially more dangerous than the large, palpable cysts. The common error that is committed in an effort to practice conservatism is to perform a limited excision of the palpable cyst which is innocent, and not remove the surrounding smaller cysts which are more likely to be complicated by the cancerous process. In the treatment of cystic disease of the breast, excision of the affected segment rather than local excision of the palpable cyst should be practiced.

Clinical Considerations

The well known tendency of cancer of the breast to disseminate early and widely renders this disease one of the most malignant of all the types of cancer with which we are familiar. Pending the acquisition of a more intimate knowledge concerning the etiological factors in the origin of mammary cancer, the most important practical problem that confronts us is the question of early diagnosis. It is an unfortunate circumstance that cancer of the breast in its early stages is an entirely painless disease. In fact, it is well known that mammary cancer may proceed through a considerable part of its natural course and reach an advanced stage without causing pain. It is because of this fact that most women fail to consult their physicians in the early stage of the disease. The medical profession teaches the laity to consult a physician the moment a palpable tumor appears in the breast. But actually, once a tumor is palpable by the patient, the disease has already reached an advanced stage. Efforts to circumvent this difficulty have led in the direction of suggesting periodic examinations, but this problem is complicated as it raises the question of how often a patient should be examined and even though a patient be examined twice annually, a cancer of the breast may have existed for four or five months before a

subsequent examination. Perhaps the most fruitful field in the prevention of mammary cancer lies in the recognition, proper interpretation, and treatment of the precancerous states, such as papillomata, Schimmelbusch's disease, and of Paget's disease of the nipple.

Any spontaneous, hemorrhagic discharge from the nipple is due either to a single papilloma or multiple papillomata, or may be due to beginning duct carcinoma. In the absence of a palpable tumor the possibility of the presence of duct carcinoma is remote, although I have observed one example in which this sign, unaccompanied by a palpable tumor, was caused by a microscopic duct carcinoma. In the presence of a palpable tumor surgical interference becomes clearly indicated. If no tumor can be palpated, transillumination of the breast frequently permits localization of the underlying lesion. When the papillomata are of microscopic dimensions transillumination fails to disclose them. The treatment of a breast, which is the seat of a hemorrhagic discharge from the nipple and in which no tumor can be felt, constitutes a difficult and perplexing problem. The choice of treatment depends upon numerous circumstances, the age of the patient being one important factor. In several examples of this type in which the patients have refused surgical interference Interstitial radiation of the breast was substituted. This procedure has resulted in a fibrosis of the lesion and a cessation of the bleeding, and I regard it as a useful procedure in selected cases.

Palpable Tumors

There is a tremendous variation in the consistency of normal breasts, and the same breast usually undergoes marked changes during various stages of the menstrual cycle. The interpretation of "lumps" in the breast and areas of localized nodularity is a difficult matter. The most important aid in the interpretation of a suspected "lump" or nodularity is to determine by very careful palpation in sitting and lying positions the condition of the remainder of the breast, and also the con-

dition of the opposite breast. Only in this manner can one establish the consistency of the remainder of the mammary tissues, and these findings constitute an important control in the patient who is being examined. The most important finding in a suspected "lump" is the presence of a localized nodularity in one breast which cannot be discovered in any other portion of the breast or in the opposite breast. Localization is the most important clinical finding in suspected lesions of the breast. The discovery, therefore, of several "lumps," or several nodularities, should immediately raise the suspicion that the condition is physiological rather than pathological, and that the condition is benign rather than malignant. It is for this reason that multiple masses in, or a multi-nodularity of, one or both breasts is usually the sign of a benign process. It is also of the greatest importance in cases in which the interpretation of the clinical findings is difficult without the opportunity of examining the patient at different stages of the menstrual cycle. By this procedure one frequently discovers that certain suspected nodularities have completely disappeared and the diagnosis at once becomes evident. The more common conditions which cause multi-nodularity are: (1) mastoplasia, (2) multiple fibroadenomata, and (3) multiple cysts.

The most important sign of cancer of the breast is the presence of a single, discrete tumor, or a localized nodularity in one breast. The absence of skin adherence and retraction of the nipple cannot be considered as evidence that cancer does not exist. The safest attitude is to regard a single, localized tumor in one breast of a woman more than twenty as cancer until proved otherwise.

Transillumination

In 1929 I first described transillumination of the breast as an aid in differential diagnosis. Other observers who have utilized this procedure have generally agreed that it is a distinct aid in the interpretation of certain lesions of the breast. During the examination it is essential that the

room be absolutely dark and that the transilluminating lamp be sufficiently powerful to penetrate the various lesions that we encounter in the mammary gland. Transillumination is a distinct help in the interpretation of the following conditions: (1) In the differential diagnosis between solid tumors and cysts containing clear fluid; (2) in the diagnosis of hematoma of the breast following trauma, and (3) in the localization of duct papillomata underlying hemorrhagic discharges from the nipple. The procedure does not differentiate between a benign and malignant solid tumor such as fibroadenoma and carcinoma. A deep-seated cyst may exhibit all the classical signs of cancer, including adherence of the overlying skin and retraction of the nipple. If the cyst contains clear fluid it will transilluminate clear, and transillumination under these circumstances is a valuable aid in differentiating between the two conditions.

A trauma to the breast may cause interstitial hemorrhage and a resulting hematoma. Frequently the mass that is thus formed exhibits skin adherence and presents the clinical picture of carcinoma. Indeed, the similarity to carcinoma is so striking that mastectomy has frequently been performed for this condition. Transillumination of a hematoma indicates a shadow that is caused by the blood pigment which has a specific appearance. The opacity is intense, irregular, and slowly fades toward the periphery. Based upon these findings alone I have withheld exploratory incision in a series of cases. Repeated transillumination under these circumstances shows a gradual diminution in the extent and intensity of the opacity and its final complete disappearance. It may require as long as three months for the shadow to disappear. These lesions are uncommon, but, when encountered, present a difficult clinical problem, in the solution of which I have found transillumination of considerable aid.

Transillumination is perhaps most useful in breasts which are the seat of a hemorrhagic discharge from the nipple. In most cases transillumination discloses opacities which indicate the site and dis-

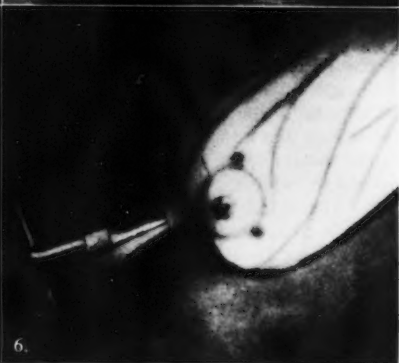
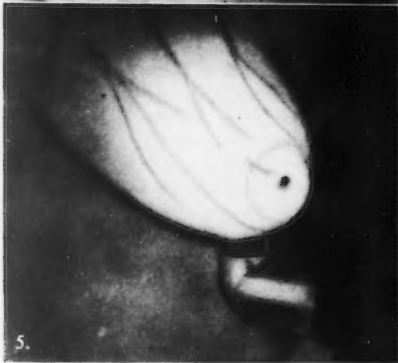
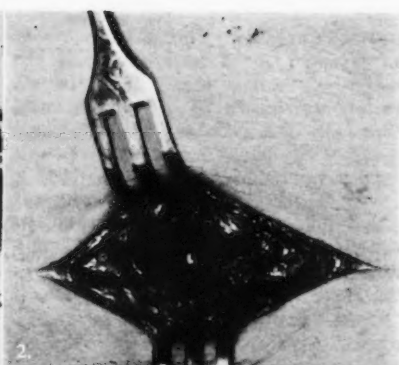


Fig. 1. Whole section of breast showing cystic disease and duct papillomata (Schimmelbusch's disease).

Fig. 3. Classical dimpling of skin caused by an underlying carcinoma.

Fig. 5. Shadow caused by a solitary, duct papilloma as seen by transillumination.

Fig. 2. Solitary blue-dome cyst of breast.

Fig. 4. Hematoma of breast as seen by transillumination.

Fig. 6. Multiple shadows due to multiple duct papillomas as seen by transillumination.

tribution of the underlying lesion. This finding in breasts in which no tumor can be palpated is of considerable help in deciding the therapeutic procedure to be adopted.

There is great anxiety among women today, concerning breast cancer and physicians everywhere must be prepared to assume an increasing responsibility. A hurried examination can readily fail to detect a tiny lump or a slight dimpling of the skin, whereas early detection of these subtle signs can be life-saving. The temptation to minimize a patient's complaints and to assume that she is cancerophobic is

great. The responsibility of dismissing a patient from your office with the good news that all is well, is a grave one, and every doctor should think seriously and ask himself, "Am I dismissing a patient who is harboring an early, curable breast cancer which I might have discovered had my examination been adequate?" These are not theoretical considerations; they are actual, daily problems which affect the lives of women and the welfare and happiness of their families. The physician's decisions concerning these problems will either save or cost the lives of thousands of women everywhere.

References to Neoplasms of the Breast in Previous Issues of CA

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CANCER CLINIC



Carcinoma of the Breast

Abstract of Practitioners' Conference, held at the New York Hospital-Cornell Medical Center. Vol. 5. New York, Appleton-Century-Crofts, Inc. 1957. Claude E. Forkner, M.D., Ed. Panel: Drs. William A. Cooper, Harry W. Burnett, Eugene J. Cohen, Herbert Conway, Cranston W. Holman, Richard Stark, Benjamin E. Marbury, and John M. Pearce.

Case 1. A 75-year-old patient sought advice because of increasing retraction of her nipple over a period of six months. There was no pain and no discharge from the nipple. There was a 2-cm., firm mass above the nipple, freely movable over the chest wall and attached to the nipple, as demonstrated by movement of the mass, causing further nipple retraction. There was slight attachment to the skin. Since routine preoperative examination of lung fields and osseous structures showed no evidence of metastases, radical mastectomy was done. Special attention was given to the type of anesthesia on account of her age and a slight hypertension—

160/100 mm. of Hg. The electrocardiogram was normal. Demerol was avoided since opiates are much more depressant in the older age groups. Premedication was given an hour before anesthesia which was started with pentothal, 2.5 per cent solution by intermittent drip, and nitrous oxide and oxygen in a semiclosed system. This anesthesia was chosen because a nonexplosive agent is necessary when electrocautery is anticipated. The primary anesthetic agent was nitrous oxide and oxygen. Blood loss was replaced to compensate fall in blood pressure. Anesthesia was maintained at a light plane so that the patient might react very shortly after the operation and so that the postoperative period of recovery might be better. Excisional biopsy showed the characteristic appearance of carcinoma on the cut surface. The tumor was hard, unlike benign lesions, and the cancer was depressed below the surrounding fat. Benign

lesions tend to bulge above the fat. After the diagnosis of carcinoma was confirmed by frozen section, radical mastectomy was performed. The absence of axillary involvement is of great importance in prognosis. The patient has twice as good a chance of doing well when the axilla is not involved.

Case 2. A 78-year-old patient was admitted to the clinic five years after radical breast operation. There were recurrences in the chest wall. Stilbestrol, 15 mg. daily, was started. Within two weeks there was moderate regression of the tumor mass and within two months there was practically complete regression down to a pea-sized cartilaginous nodule which showed no further change. For the following three and a half years this patient was maintained on stilbestrol until the age of eighty-one when she died of coronary occlusion. If estrogen therapy had failed, androgens would have been tried. In a younger woman androgens would be used at the start.

Case 3. This patient at the age of thirty had a radical operation followed by roentgen-ray therapy. Two and a half years later she developed pain in her right hip and a limp on walking. A metastatic lesion was shown by roentgenogram in the right ilium. Testosterone propionate, 50 mg., was given three times weekly and within two weeks there was relief of pain and the limp disappeared. Surgical castration was performed. One year later roentgenogram showed an increase in the osteolytic lesion. Even though the patient felt entirely well, roentgen-ray therapy was given in conjunction with testosterone propionate. Eight months later a roentgenogram showed sclerosis and increased density of bone. The patient is now five years postoperative and is feeling entirely well. Bilateral adrenalectomy is being reserved as later therapy. No hard and fast rule can be given for treating any individual patient.

Accurate and detailed history and thorough physical examination are of great importance in the early and correct diagnosis of carcinoma of the breast. Inspection and palpation are often diagnostic. If

the physician will be alert in the diagnosis of breast tumors, if he will recognize the fact that the solitary nodules are the important ones, if he will recommend and teach the patient self-examination of the breast, and if he will recommend excision of any questionable lesion early in the course of the disease, more of these patients will be cured. Hope for the breast-cancer patient lies in earlier diagnosis and more extensive surgical procedures. If a patient has a painful breast, or if both breasts are painful or sensitive in relation to her periods, or if she has a new lump that is tender, the lump is much more likely to be innocent and related to cystic mastitis than it is to be malignant. All suspicious lumps in the breast are examined microscopically after excisional biopsy. The entire tumor is removed, and not cut across, in doing a biopsy.

Carcinoma of the breast is more common in the upper outer quadrant, from which region it metastasizes to the axillary lymph nodes, the group most accessible to the surgeon. These tumors may be cured by the classical radical mastectomy, which includes, in addition to removal of the entire breast and pectoral muscles, dissection of the upper and lower inner quadrants of the axilla. The lymphatics draining into the lymph nodes posteriorly toward the chest and along the internal mammary vessels are much less accessible. The deeper the lymph-node metastases occur in the axilla, the poorer the prognosis. In view of what we know about metastases, irradiation that does not include the supraclavicular region, the axilla, the internal mammary chain, and the mediastinum cannot be considered adequate. In addition, this treatment must be given in adequate dosage. The patient may be benefited even if the irradiation does not destroy all the cancer cells, as local fibrosis may limit the disease and allow the patient to be symptom-free or five or even ten years. Irradiation is useful in recurrences that are small and confined to a local area; but when soft-tissue metastases are extensive it is impractical. Radiation castration and endocrine administration may be of value in the more advanced cases. Many

new steroids are being tested in advanced breast cancer, and early important changes in hormone therapy may be expected.

Carcinomas of the breast may be classified as noninvasive and invasive. The non-invasive are intraductal, consisting of large masses of tumor cells confined to the ducts and commonly with necrosis of the central portion. These intraductal cancers do not metastasize.

The invasive cancers may be scirrhus, medullary, or diffuse anaplastic. The scirrhus is the most common type and has the poorest prognosis. It is characterized by the presence of large amounts of hyaline, fibrous tissue tending to compress the tumor cells and to depress the cut surface of the tumor beneath the fat.

The medullary type is less common and has a better prognosis. It may be large with very little connective tissue or stroma and with adenomatous tissue showing gland formation.

The diffuse, anaplastic type is the rarest of the three invasive types and has very poor prognosis. The tumor cells vary greatly in size and shape. Diffuse, anaplastic carcinomas are classified into colloid or mucoid and squamous-cell carcinomas. Small metastases can be shown in a considerable number of apparently innocent axillary nodes by serial microscopic sections.

Three methods of management of carcinoma of the breast are current: Halsted radical mastectomy, extension of the Halsted operation to include resection of supraclavicular and internal mammary lymph nodes, and simple mastectomy with postoperative irradiation.

Twenty-five years ago 80 per cent of patients with carcinoma of the breast had axillary-node involvement when first seen. Today, this figure has been reduced to 48 to 63 per cent, due to earlier diagnosis.

Radical surgery reduces the incidence

of local recurrence and increases the percentage of five-year survivals. In the New York Hospital series 25 per cent of patients with, and 16 per cent of those without, axillary metastases had postoperative recurrences. The five-year cure rate of patients with axillary metastases was 27 per cent, and without axillary metastases, 62 per cent. Patients with tumors less than 3 cm. in diameter had a recurrence rate of 24 per cent, and those with tumors more than 3 cm. in diameter, 46 per cent. Only 1.6 per cent of patients who survived five or more years with no evidence of recurrence had subsequent recurrence of tumor. Ninety per cent of patients developing local recurrences died within two years. Seventy-three per cent of recurrences are in and around the operative incision, indicating the desirability of more radical excision of skin and subcutaneous fat.

Adequate data are not available for evaluation of the superradical procedure. Recommended treatment at the New York Hospital is radical mastectomy with axillary dissection and a large skin graft. In the presence of metastases thorough roentgen-ray irradiation is given to the supraclavicular, axillary, internal mammary, and mediastinal chains of lymph nodes. Endocrine treatment is employed palliatively in far advanced cases not suitable for surgery, roentgen-ray, or combined therapy. Androgens are used at any age and estrogens at age sixty-five or ten years after the menopause. Sixty per cent of patients with metastatic or recurrent carcinoma of the breast are helped by this therapy. There is no regression of the tumor in from 20 to 30 per cent of such cases. Surgical or roentgen-ray castration is at times a valuable palliative procedure. Bilateral adrenalectomy may be considered in selected cases but is still experimental.

Erratum

Figures 2 and 4 were interchanged on page 155 of the September issue of *CA*.



new developments in cancer

Cigarettes and Lung Cancer . . .

Drs. E. Cuyler Hammond and Daniel Horn of the American Cancer Society have reported that their four-year study of the smoking habits and fate of 188,000 aging American men (11,870 of them dead during the course of the study) indicates that: 1) light cigarette smokers have a death rate 34 per cent higher than the nonsmokers, and heavy smokers 123 per cent higher; 2) quitting smoking lowers the risk of death—particularly for those who have quit for ten or more years; 3) heavy smokers have a death rate from coronary artery disease 141 per cent higher than the nonsmokers; 4) heavy smokers have a lung cancer death rate 64 times that of nonsmokers; and 5) while cigarette smokers run an elevated risk of death from several causes, the risk is the same for smokers and nonsmokers in accidents, violence, suicide, chronic rheumatic fever, hypertensive heart disease, other hypertensive diseases, nephritis, nephrosis, diabetes, leukemia, and cancers of the rectum, colon, and brain.

Colcemide . . .

Dr. Louis K. Alpert and others at George Washington University have re-

ported that colcemide, an antimitotic extract of the plant, *Colchicum autumnale*, gave favorable results in six patients with chronic myeloid leukemia. It brought the white-cell counts down to normal and shrank enlarged spleens and livers. In other forms of cancer, colcemide was less impressive. It gave a brief remission in some cases of Hodgkin's disease and was ineffective in other blood and solid neoplasms.

Carcinogen Test? . . .

Frog tadpoles are being tested as "carcinogen detectors" at the Philadelphia Institute for Cancer Research—and, so far, with interesting results. Dr. Elizabeth Green and Mrs. Constance Herdeck grow the four- or five-day-old tadpoles in finger bowls. Water-soluble derivatives of known carcinogens are placed in the bowls for a few days. Following this experience, tadpole tail slices show an astonishing variety of cells—as many as 75 per cent of the cells are giants, some of them with several nuclei, each of which may contain up to thirty-two nucleoli and multiple chromosomes. Other cells are dwarf. These abnormalities frequently persist through many weekly tail slicings. Few of the tadpoles survive to the frog stage, although

they are put in spring water following their carcinogenetic bath. Noncarcinogenic compounds which affect growth, like colchicine and anthracene protein conjugates, have relatively little effect on the cells.

Gold Increases Survival . . .

Radon and radioactive gold, injected preoperatively into loose tissues around the uterus, appear to be increasing the survival rate of patients with cancer of the uterine cervix. In several series the procedure has yielded a survival double that achieved by conventional methods. The technique has been followed for six years by Drs. Willard M. Allen, Alfred I. Sherman, and A. Norman Arneson of the Washington University School of Medicine. The treatment calls for injecting radioactive gold in colloidal suspension into loose tissues around the uterus and implanting radon pellets in the vagina and cervix. Usually a month or two later, a hysterectomy is done. The scientists have reported that three or more years following treatment these percentages of patients are alive and without evidence of disease: Stage 0, almost 100; Stage I, 87.6; Stage II, 80; Stage III, 50. There is no salvage of Stage IV cases. Examination of tissues removed at operation showed that the gold seeped into lymphatic channels and destroyed escaping cancer cells.

Bacterial Polysaccharides . . .

Dr. Richard C. Putnam and others (Lankenau) have reported results of treating 129 cancer patients with intravenous "P" and "O" fractions of bacterial polysaccharides, those toxic and tantalizing preparations which cure some rat transplanted sarcomas and provide dramatic but temporary regressions of some human cancers. The most recent score: sixteen of twenty-four lymphoma patients showed tumor regression, often with lengthy remission; eighteen of fifty-six sarcomas showed some regression;

carcinoma and melanoma were questionably affected. The drugs often were synergistic with X rays. Toxic effects of the more recent fractions resembled those of earlier preparations—high fever and hypotension, nausea, vomiting, malaise, and chills, frequently abating in about twenty-four hours. In responsive patients, tumor softening, shrinkage, and hemorrhage usually were seen within twenty-four hours.

Narcosis . . .

Another group of antagonists, including 6-azauracil, have been reported by Dr. A. D. Welch and others of Yale University to have a variety of unwanted side effects. In humans they produce drowsiness and electroencephalographic disturbances within a few days. They depress weight gain in adult mice and when given in water, kill weanling mice. Continued administration to dogs caused weight loss, diarrhea, anorexia, and death. Clinicians at the National Cancer Institute reported that about one-third of adults and children with acute leukemia received temporary benefit from 6-azauracil.

To Hysterectomize or Not to? . . .

Hysterectomy can be postponed safely in many cases of cervical carcinoma in situ in women of child-bearing ages, according to the results of a study at the State University of New York, College of Medicine, Brooklyn. Dr. John G. Masteron has reported a substantial safety factor in a four-year follow-up study of twenty-five such cases. The average age was thirty years. Of the twenty-five women, fifteen were alive and well with no progression of their cancers; five had been given radical hysterectomies or intensive X-irradiation when the cancers became invasive; two were given moderately radical operations when the cancers became suspiciously active; and three patients dropped from the study prematurely but still in good health. Five of the women have had one or more pregnancies.

sixty species shows a good correlation between brain weight and life span--and an even better relationship between combined brain and body weights and life span.

McLaren and Takahashi (U. of Calif.) have learned that the virus is protected from radiation effects by its protein coat. It took only one-sixth the dose of ultraviolet to inactivate the uncoated nucleic acid as it did to inactivate the entire tobacco mosaic virus.

Finkel and others (Argonne) have found that deuterium, as a substitute for hydrogen, is not highly toxic to biological systems. Mice tolerated up to 40 per cent D₂O as a substitute for drinking H₂O for more than two months. About 40 to 50 per cent of the body fluids was D₂O, and deuterium was found abundantly in solid tissues.

Using new age-correcting statistical techniques, Messinger (U. of Calif.) estimated that 62 per cent of localized breast cancer patients from any age group are alive ten years after diagnosis.

Partridge, Nelson, and Giles (Yale) have found that genes inactivated by radiation can be restored by either more radiation or mating with another genetic type. The subject in these studies was a neurospora gene-controlling enzyme involved in AMP synthesis.

Daniels and Vogel (Argonne) gave amoebas twice the lethal dose of radiation. They then added to the irradiated culture protoplasm from nonirradiated amoebas. About 91 per cent of the treated animals were saved--they survived to the end of the experiment, and most of them had prolific offspring. The antiradiation fraction appears to reside in the lighter portion of the protoplasm.

Neonatally castrated male mice developed pituitaries 20 per cent heavier than noncastrate control pituitaries, Runner and Dickie (Bar Harbor) reported. But, assays showed the gonadotropin content of the large pituitaries was only normal. These observations are contrary to the findings in other species, and they may indicate that, in these mice, the adrenals satisfactorily assumed the endocrine function of the gonads.

Stadler and Gowen (Iowa State College) have found that while the life span of male mice shortens with radiation, the life span of females increases under low dosages (up to 80 r) and shortens dramatically under exposures of 160, 320, 640, and 960 r. Pregnancies and litter sizes decline with low dosage whole-body irradiation--20 r reduces the normal five pregnancies to three, and with a dosage of 80 r only

one-half of the female mice ever become pregnant.

Allen and Kahn (Army Chemical Corps) report that rice polishings have prevented virus disease in plants. Pinto bean plants, infected with tobacco mosaic virus and then dropped into a solution containing rice polishings, grew and remained healthy in most cases while untreated plants died or were severely damaged. The investigators are speculating as to whether the polishings, an abundant by-product of rice milling, might be used effectively against virus diseases of plants, animals, and man.

Macklin (Ohio State) says that mortality rates from breast cancer are about 60 per cent higher in single than among married women and that the risk decreases with the increasing number of offspring. She believes that genetic factors in human breast cancer are at least as important as the environmental.

Roberts, Wipf, and Struckmeyer (U. of Wis.) have suppressed tumor growth in plants and animals with a naturally occurring plant hormone, antiauxin. Because antiauxin is fat-soluble, the researchers suggest that tumor origin and the hormone's activity might lie in the field of fatty metabolism. The hormone may be a protective or repair mechanism. Tested in very dilute solution against mouse tumors induced with methylcholanthrene and 3,4-benzpyrene, antiauxin not only inhibited tumor growth but also suppressed the swelling of lymph nodes, kidneys, and spleens.

Bender (Johns Hopkins) has warned that, according to his calculations of radiation damage on cultured human kidney cells, present standards of "safe" dosages are not at all safe. "In fact," he said, "the present experiments, taken by themselves, lend great weight to the belief of many geneticists that there is no 'safe' dose of radiation."

Various . . . one of the most exciting developments in current virus work is the finding by Burmester (East Lansing U.S. Dept. of Agric.) that a high percentage of chicks can be protected against lymphomatosis by inoculating mother hens with the killed viruses of the disease. The immunity, passed from mother to offspring, tides the chicks over their susceptible period until they develop their own immunity. The procedure, if confirmed by further experiments, will have enormous commercial value. Dmochowski and Grey (M. D. Anderson Hospital) have made electron micrographs of the viruses and have found a startling similarity between them and particles found in leukemic human and mouse tissues.

COMING MEDICAL MEETINGS

Date 1958	Meeting	City
Mar. 3-6	New Orleans Graduate Medical Assembly	New Orleans
Mar. 4-7	Chicago Medical Society	Chicago
Mar. 10-13	International College of Surgeons	Los Angeles
Mar. 23-26	Aero Medical Association	Washington, D. C.
Mar. 24-26	New England Hospital Assembly	Boston
Mar. 27-29	American Radium Society	Hollywood Beach (Florida)
Mar. 29-30	American Psychosomatic Society	Cincinnati
Apr. 7-10	International Symposium on Radio- active Isotopes in Clinical Medicine and Research	Bad Gastein (Austria)
Apr. 11-13	American Association for Cancer Research	Philadelphia
Apr. 13-18	John A. Andrew Clinical Society	Tuskegee Institute
Apr. 13-19	American Society for Experimental Pathology	Philadelphia
Apr. 16-18	American Surgical Association	New York City
Apr. 17-19	American Association of Railway Surgeons	Chicago
Apr. 19-25	Industrial Medical Association	Atlantic City
Apr. 21-23	American College of Obstetricians and Gynecologists	Los Angeles
Apr. 21-26	American Academy of Neurology	Philadelphia
Apr. 24-26	International Society of Internal Medicine	Philadelphia
Apr. 24-26	American Association of Pathologists and Bacteriologists	Cleveland
June 23-27	American Medical Association	San Francisco
June 25- July 1	International Congress of Urology	Stockholm
June 29- July 3	American Proctologic Society	Los Angeles
July 6-12	7th International Cancer Congress	London

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